CHAPTER 4

Ni-Catalyzed Intramolecular C–O Bond Formation: Synthesis of Cyclic Enol Ethers†

4.1. Introduction

Transition metal-catalyzed cross-coupling reactions have served a powerful tool for efficient carbon–carbon and carbon–heteroatom bond formations over the past several decades.[1] Recently, nickel catalysis has emerged in the synthetic community as an exceptionally useful strategy for cross-coupling.[2] Although tremendous advances in nickel-catalyzed carbon–carbon bond formation have been achieved (e.g., Negishi, Suzuki, Stille, Kumada, Hiyama couplings),[3] nickel-catalyzed carbon–oxygen bond forming processes have proven significantly more challenging. The rationale behind this is that reductive elimination of Ni(II) alkoxide complexes is often cited as being significantly challenging even at elevated temperatures.[4] To circumvent this challenge, stoichiometric oxidation of Ni(II) to the less stable Ni(III) analogs has been required. Additionally, reductive elimination of Ni(II) alkoxides is

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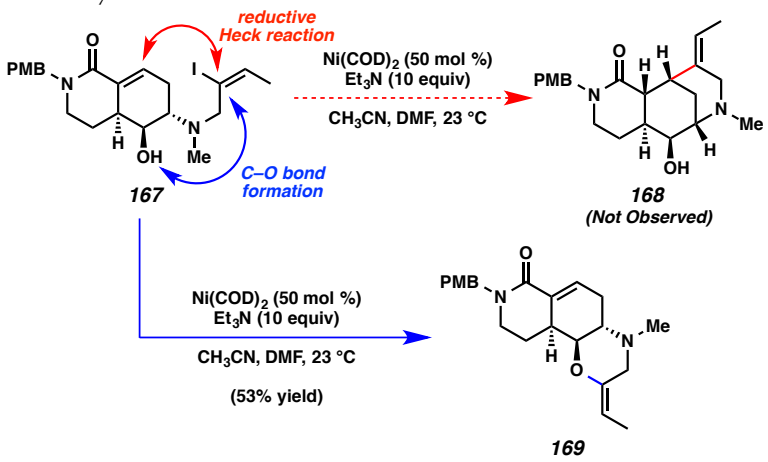
reported to be endothermic via computational analysis. This is in contrast to that of Pd(II) alkoxides, which are exothermic.[5] In 1997, Hartwig and co-workers developed the first nickel-catalyzed cross-coupling between electron-deficient aryl halides and pre-formed sodium alkoxides or sodium siloxides.[6] In 2014, the Ranu group reported a copper-assisted nickel-catalyzed coupling of phenol derivatives and vinyl halides.[7] However, both of these reactions require high temperatures, and the scope of the nucleophiles is limited to pre-formed alkoxides or phenols. Most recently, MacMillan and co-workers developed the nickel-catalyzed intermolecular cross-coupling of aryl bromides and aliphatic alcohols in the presence of light and a photoredox catalyst.[8] Importantly, MacMillan and co-workers could not observe their desired C–O coupling products in the absence of either the photocatalyst or light. Although Pd- or Cu-catalyzed C–O bond forming reactions have been significantly developed, most of these reactions require high temperature that can limit their utility in the synthesis of multifunctional complex molecules. Moreover, the vast majority of these examples are for aryl ether synthesis, not enol ether synthesis.[9,10,11] To our knowledge, a mild and efficient nickel-catalyzed intramolecular cross-coupling cyclization between aliphatic hydroxyl nucleophiles and tethered vinyl halides is unprecedented.

4.2. Results and Discussion

In the course of an alkaloid synthesis effort, we attempted a nickel-catalyzed reductive Heck reaction of vinyl iodide **167** with the aim of producing tricycle **168** (Scheme 4.2.1, red arrows).[12] Surprisingly, instead of the desired intramolecular C–C bond-forming reaction, a C–O bond-forming cyclization between the vinyl iodide and the free hydroxyl group furnished morpholine derivative **169** (Scheme 4.2.1, blue arrows). Given the lack of precedent in the literature for such a transformation with

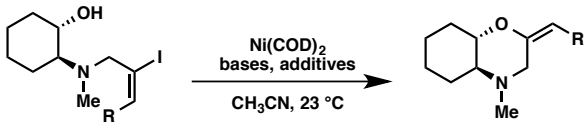
nickel catalysis, we set out to explore the generality of this reaction. Herein, we describe the first nickel-catalyzed cycloetherification of aliphatic alcohols with pendant vinyl halides.

Scheme 4.2.1. *Ni-Catalyzed C–O Bond Formation*



Given this interesting preliminary data, we chose aminocyclohexanols **170a** and **170b** as simplified substrates for reaction optimization studies (Table 4.2.1). Our initial reaction conditions afforded the corresponding morpholines **171a** and **171b** in 53% and 42% yield, respectively (entries 1 and 2). A wide variety of bases and additives were investigated to improve the yield and catalytic efficiency (entries 3–10). We found triethylamine to be superior to others examined (entries 3–5). The use of a 1:1 mixture of triethylamine and DABCO allowed etherification in 69% yield with reduced catalyst loading (i.e., 20 mol % $Ni(COD)_2$, entry 6). Gratifyingly, the use of 2 equiv of zinc powder as an additive resulted in a significant improvement in yield (84%) with only 5 mol % of $Ni(COD)_2$ (entry 10).[13,14,15,16,17]

Table 4.2.1. *Optimization of reaction parameters*[a]



R = Me (*170a*)
R = H (*170b*)

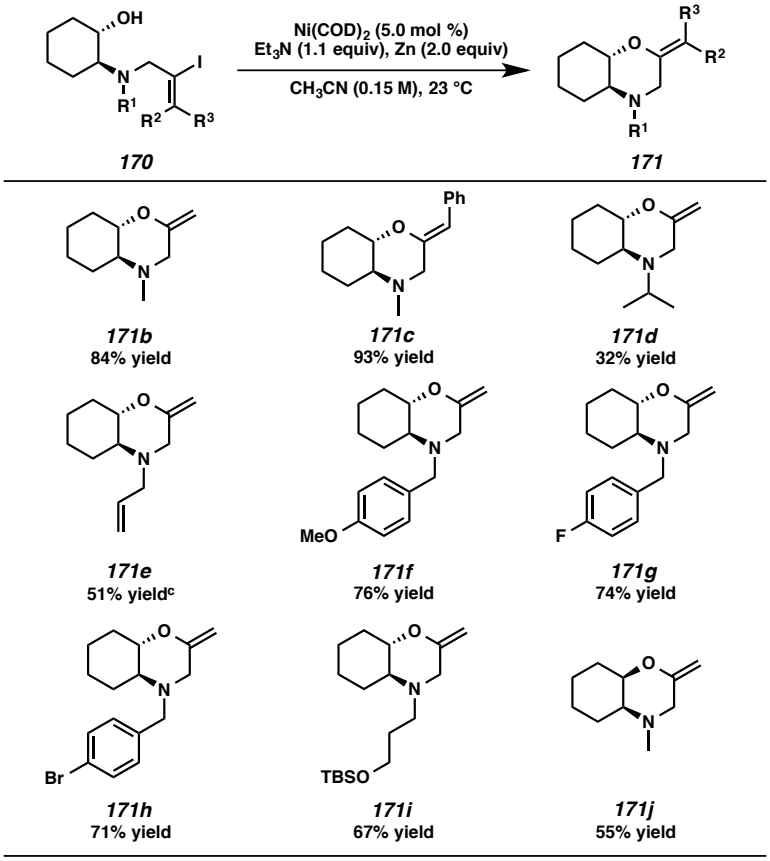
R = Me (*171a*)
R = H (*171b*)

entry	substrate	conc (M)	Ni mol %	base	additive	yield (%)[b]
1[c]	*170a*	0.02	50	Et_3N (10 equiv)	–	53
2[c]	*170b*	0.02	50	Et_3N (10 equiv)	–	42
3[c]	*170a*	0.02	35	Et_3N (10 equiv)	–	42[d]
4[c]	*170a*	0.02	35	Cs_2CO_3 (3.0 equiv)	–	30[d]
5[c]	*170a*	0.02	35	K_3PO_4 (3.0 equiv)	–	34[d]
6	*170b*	0.10	20	Et_3N (1.0 equiv)	DABCO (1.0 equiv)	69
7	*170b*	0.10	20	Et_3N (1.0 equiv)	CsF (1.0 equiv)	51
8	*170a*	0.04	20	DABCO (1.0 equiv)	–	24
9	*170a*	0.04	20	DABCO (2.0 equiv)	–	50[d]
10	*170b*	0.15	5	Et_3N (1.1 equiv)	Zn (2.0 equiv)	84

[a]Reactions were performed in a N_2-filled glove box. [b]Yield of isolated product. [c]DMF (0.04 M) was used as a co-solvent. [d]The reaction proceeded with incomplete conversion of starting material.

With optimized conditions in hand, we investigated the substrate scope of the transformation (Table 4.2.2). In addition to simple vinyl iodides (e.g., **170b**, R^1 = Me, R^2 = H, R^3 = H),[18] a (*Z*)-styrenyl iodide (i.e., **170c**, R^1 = Me, R^2 = H, R^3 = Ph)[19] furnished vinyl ether **171c** in high yield and without loss of olefin stereochemical fidelity. Aminocyclohexanols bearing isopropyl and allyl substituents on nitrogen afforded the corresponding products in reduced yields (**171d** and **171e**). Electronically variable benzyl groups were compatible under the reaction conditions, and even an aryl bromide was well tolerated (**171f–171h**). Additionally, a silyl ether group remained intact, generating substituted morpholine **171i** in good yield. Moreover, we discovered that a *cis*-aminocyclohexanol derived substrate was competent in the reaction, providing the *cis*-fused bicyclic product **171j**.[20,21]

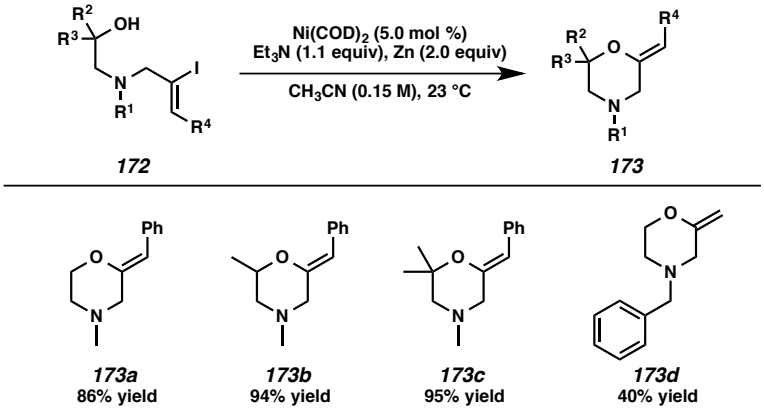
Table 4.2.2. *Intramolecular cross-coupling of amino-cyclohexanols*[a,b]



[a] Reactions were performed in a N_2-filled glove box. [b] Yield of isolated product. [c] 96 h.

To our delight, we found that the nickel-catalyzed intramolecular etherification reactions also proceeded with linear aminoalcohol substrates to generate monocyclic morpholine derivatives in moderate to high yields (Table 4.2.3). The steric environment of the alcohol fragment did not hinder the performance, as substrates containing primary, secondary, or highly congested tertiary hydroxyl nucleophiles furnished the corresponding cyclic vinyl ethers in excellent yields (**173a**–**173c**). Finally, a benzyl-substituted linear aminoalcohol substrate was transformed to the desired vinyl ether in modest yield (**173d**).

Table 4.2.3. *Intramolecular cross-coupling of linear aminoalcohols*[a,b]

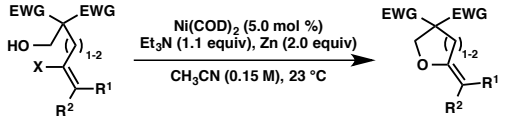


[a] Reactions were performed in a N_2-filled glove box. [b] Yield of isolated product.

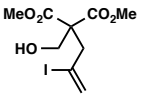
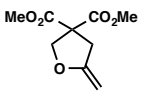
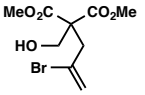
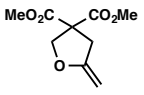
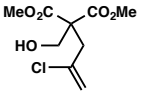
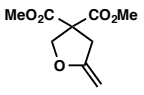
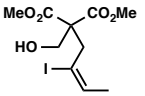
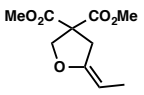
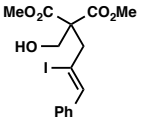
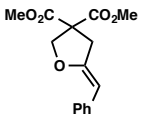
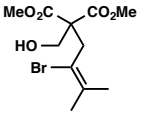
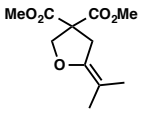
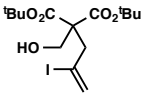
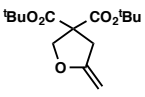
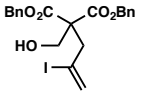
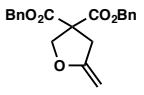
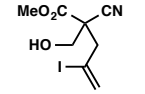
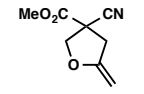
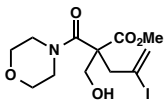
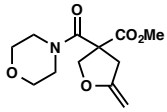
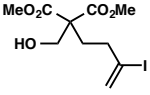
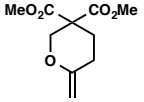
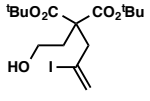
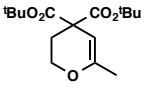
We were pleased to discover that additional acyclic substrates undergo the nickel-catalyzed carbon–oxygen cross-coupling to furnish alkylidene tetrahydrofurans and dihydropyrans (Table 4.2.4). Intramolecular etherification of vinyl iodide **174a** furnished the cyclic ether **175a** in good yield in only 1 h (entry 1). Although less reactive, a vinyl bromide also fared well in the reaction, affording the corresponding product in 52% yield after 12 h (entry 2). Unfortunately, attempts to employ a vinyl chloride as the coupling partner led predominantly to recovery of starting material (entry 3). Mono-methyl and mono-phenyl substituted vinyl iodides (**174d** and **174e**)[22] afforded the desired ethers (**175d** and **175e**) in good yields with retention of olefin stereochemistry (entries 4 and 5). Gratifyingly, tetrasubstituted vinyl bromide **174f**[23] furnished the corresponding tetrahydrofuran product **175f** in excellent yield (entry 6). Di-*tert*-butyl and dibenzyl malonates (**174g** and **174h**) were tolerated under the standard reaction conditions to afford the desired ethers (**175g** and **175h**) in good yields (entries 7 and 8). Additionally, carbon–oxygen bond formations were achieved with nitrile- and amide-containing substituents in 61% and 70% yield, respectively (entries 9 and 10). Formation of a six-membered cyclic vinyl ether (**175k**) from substrate **174k** was found to be challenging with only low levels of conversion (entry

11). Interestingly, cycloetherification of **174l** did indeed produce a pyran derivative in good yield, but only isomerized product **175l** was isolated (entry 12).[24,25,26]

Table 4.2.4. *Synthesis of substituted tetrahydrofuran and dihydropyran rings*[a]



174 *175*

entry	substrate	product	time (h)	yield (%)[b]
1	 *174a*	 *175a*	1	87
2	 *174b*	 *175a*	12	52
3	 *174c*	 *175a*	60	–[c]
4	 *174d*	 *175d*	2	87
5	 *174e*	 *175e*	12	91
6	 *174f*	 *175f*	48	98
7	 *174g*	 *175g*	1	87
8	 *174h*	 *175h*	1	66
9	 *174i*	 *175i*	12	61
10	 *174j*	 *175j*	1	70
11	 *174k*	 *175k*	72	–[c]
12	 *174l*	 *175l*	12	76

[a] Reactions were performed in a N_2-filled glove box. [b] Yield of isolated product. [c] Low conversion.

4.3. Conclusion

In conclusion, a highly efficient, mild, and operationally simple nickel-catalyzed intramolecular carbon–oxygen bond-forming reaction between vinyl halides and aliphatic alcohols has been developed. We discovered that zinc powder plays an important role in improving catalyst turnover and isolated yields. The reaction is tolerant of many functional groups, affording various cyclic vinyl ethers in good to excellent yields. This work further expands the capability of nickel catalysis in the context of small molecule chemical synthesis. Additional studies are ongoing to expand the scope of the reaction, to understand the mechanism, and to deploy the cyclization in the context of a complex molecular target.[27] These efforts will be reported in due course.

4.4. Experimental Methods and Analytical Data

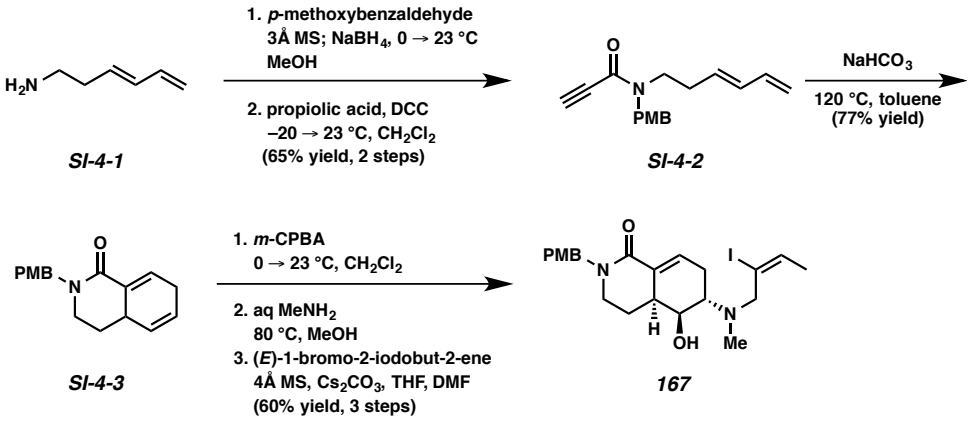
4.4.1. Materials and Methods

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-MS. THF, Et_2O, CH_2Cl_2, toluene, benzene, CH_3CN, and dioxane were dried by passage through an activated alumina column under argon. Purified water was obtained using a Barnstead NANOpure Infinity UV/UF system. Brine solutions are saturated aqueous solutions of sodium chloride. Commercially available reagents were purchased from Sigma-Aldrich, Acros Organics, TCI, Oakwood chemicals, Strem, or Alfa Aesar and used as received unless otherwise stated. $Ni(COD)_2$ and NiI_2 were purchased from Strem. $NiBr_2$(dme) was purchased from Aldrich. Zinc dust

or powder purchased from Aldrich worked well for the reaction but zinc powder (99.999%) purchased from Strem gave poor conversion. Reaction temperatures were controlled by an IKAmag temperature modulator unless otherwise indicated. Glove box manipulations were performed under a N_2 atmosphere. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, $KMnO_4$ or PMA (phosphomolybdic acid) staining. Silicycle Silia*Flash* P60 Academic Silica gel (particle size 0.040-0.064 mm) was used for flash column chromatography. ^{1}H NMR spectra were recorded on a Varian Mercury 300 MHz, a Bruker AV III HD 400 MHz spectrometer equipped with a Prodigy liquid nitrogen temperature cryoprobe, Varian Inova 500 MHz, and 600 MHz spectrometers and are reported relative to residual $CHCl_3$ (δ 7.26 ppm), $CHDCl_2$ (δ 5.32) or C_6HD_6 (δ 7.16 ppm). ^{13}C NMR spectra are recorded on a Varian Mercury 300 MHz, a Bruker AV III HD 400 MHz spectrometer equipped with a Prodigy liquid nitrogen temperature cryoprobe, Varian Inova 500 MHz, and 600 MHz spectrometers (75 MHz, 126 MHz, and 151 MHz, respectively) and are reported relative to $CHCl_3$ (δ 77.16 ppm), $CHDCl_2$ (δ 53.84) or C_6HD_5 (δ 128.06 ppm). ^{19}F NMR spectra are recorded on a Varian Mercury 300 MHz (at 282 MHz). ^{19}F NMR spectra are reported relative to $CFCl_3$(δ 0.0 ppm). Data for ^{1}H NMR are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d= broad doublet, app = apparent. Data for ^{13}C are reported in terms of chemical shifts (δ ppm). IR spectra were obtained using a Perkin Elmer Paragon 1000 spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using JEOL JMS-600H High Resolution Mass Spectrometer in fast atom bombardment (FAB+) or electron

ionization (EI+) mode, or Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed ionization mode (MM: ESI-APCI+).

4.4.2. Experimental Procedures



To a solution of amine **SI-4-1** (6.66 g, 68.5 mmol, 1.00 equiv), which was prepared according to the literature procedure[1], in MeOH (171 mL) were added *p*-methoxybenzaldehyde (10.0 mL, 82.3 mmol, 1.20 equiv) and 3Å MS (18.8 g). The reaction mixture was stirred at 23 °C for 17 h. Then, $NaBH_4$ (5.20g, 0.137 mol, 2.00 equiv) was added to the solution at 0 °C. The solution was stirred at 23 °C for 12 h. After the reaction was done, water (40 mL) was added at 0 °C. The aqueous phase was extracted with EtOAc (3 x 80.0 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give the PMB-amine, which was used without further purification.

A solution of propiolic acid (4.64 mL, 75.4 mmol, 1.10 equiv) in CH_2Cl_2 (343 mL) was cooled to 0 °C. DCC (15.6g, 75.4 mmol, 1.10 equiv) and the PMB-amine (68.5

[1] (a) Miller, C. A.; Batey, R. A. *Org. Lett*. **2004**, *6*, 699–702. (b) Grieco, P. A.; Galatsis, P.; Spohn, R. F. *Tetrahedron* **1986**, *42*, 2847–2853. (c) Nieto-García, O.; Alonso, R. *J. Org. Chem*. **2013**, *78*, 2564–2570.

mmol, 1.00 equiv) were added to the reaction mixture sequentially. The mixture was warmed to 23 °C and stirred for 30 min. The solvent was evaporated and the residue was purified by flash column chromatography (1:4 EtOAc:hexanes) on silica gel to give amide **SI-4-2** (12.0g, 65% yield, 2 steps).

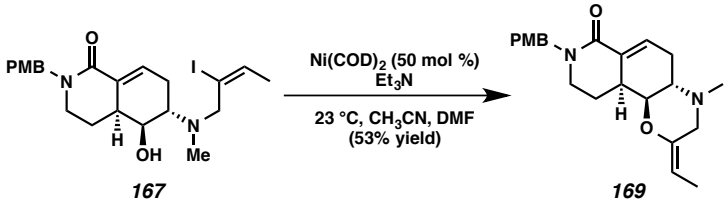
To a stirred solution of amide **SI-4-2** (12.0 g, 44.6 mmol, 1.00 equiv) in toluene (558 mL) was added solid $NaHCO_3$ (4.50g, 53.5 mmol, 1.20 equiv). The reaction mixture was heated to 120 °C for 48 h. After the reaction was done, water (200 mL) was added. The aqueous phase was extracted with EtOAc (3 x 120 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:4 EtOAc:hexanes) on silica gel to give lactam **SI-4-3** (9.25g, 77% yield).

To a stirred solution of lactam **SI-4-3** (339 mg, 1.26 mmol, 1.00 equiv) in CH_2Cl_2 (6.30 mL) at 0 °C was added *m*-CPBA (≤77%, 1.89 mmol, 424 mg, 1.50 equiv), and the mixture was stirred for 3 h at 23 °C. The reaction mixture was quenched with sat. $NaHSO_3$ and sat. $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2 (3 x 6.00 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to furnish the epoxide, which was used without further purification.

To a solution of epoxide (1.26 mmol, 1.00 equiv) in MeOH (6.30 mL) was added aq $MeNH_2$ (40 wt.% in H_2O, 12.6 mmol, 10.9 mL, 10.0 equiv). The reaction mixture was stirred at 80 °C for 12 h. After the reaction was done, water (6.00 mL) was added. The aqueous phase was extracted with EtOAc (3 x 8.00 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to afford the aminoalcohol, which was used without further purification.

To a solution of the aminoalcohol (1.26 mmol, 1.00 equiv) in THF (3.15 mL) and DMF (3.15 mL) were added 4Å MS (443 mg), (*E*)-1-bromo-2-iodobut-2-ene (411 mg, 1.58 mmol, 1.25 equiv) and Cs_2CO_3 (415 mg, 1.27 mmol, 1.01 equiv) at 23 °C. The reaction mixture was stirred at 23 °C for 24 h. The resulting suspension was filtered and washed with EtOAc (5.00 mL). The combined organic phases were extracted with EtOAc (3 x 6.00 mL). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (2:1 EtOAc:hexane) on silica gel to give vinyl iodide **167** (375 mg, 60% yield, 3 steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 6.75 (dt, *J* = 6.7, 2.1 Hz, 1H), 6.47 – 6.41 (m, 1H), 4.71 (d, *J* = 14.4 Hz, 1H), 4.41 (d, *J* = 14.4 Hz, 1H), 3.96 – 3.89 (m, 2H), 3.80 (s, 3H), 3.35 – 3.27 (m, 2H), 3.20 (d, *J* = 13.6 Hz, 1H), 3.11 (d, *J* = 13.6 Hz, 1H), 2.99 – 2.91 (m, 1H), 2.61 (td, *J* = 10.7, 4.4 Hz, 1H), 2.39 – 2.26 (m, 2H), 2.22 (s, 3H), 2.20 – 2.14 (m, 1H), 1.74 (d, *J* = 7.1 Hz, 3H), 1.56 – 1.45 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.3, 159.1, 139.0, 133.7, 130.3, 129.6, 129.5, 114.1, 103.3, 66.8, 60.1, 57.3, 55.4, 49.7, 46.9, 39.3, 35.6, 23.8, 22.3, 17.1; IR (Neat Film NaCl) 3416, 2927, 1663, 1613, 1512, 1454, 1246, 1175, 1034, 817, 732 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{22}H_{30}IN_2O_3$ $[M+H]^+$: 497.1296; found: 497.1296.



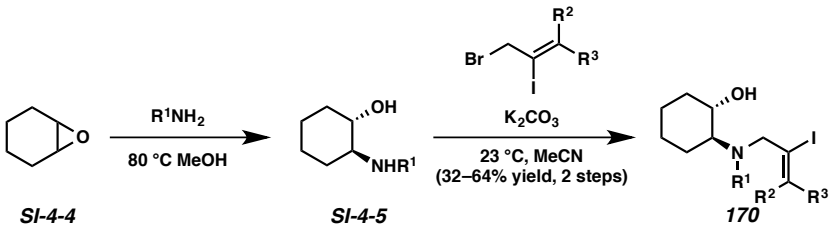
167 *169*

To a solution of vinyl iodide **167** (20.0 mg, 0.0402 mmol, 1.00 equiv) and Et_3N (56.0 μL, 0.402 mmol, 10.0 equiv) in CH_3CN (2.01 mL) and DMF (1.01 mL) in a

scintillation vial at 23 °C was added $Ni(COD)_2$ (6.00 mg, 0.0201 mmol, 0.50 equiv) in a nitrogen-filled glove box. The reaction mixture was stirred at 23 °C for 120 min, and then BHT (18.0 mg, 0.0804 mmol, 2.00 equiv) was added. After being stirred for 20 min, the vial was removed from the glovebox and uncapped. Saturated $NaHCO_3$ aqueous solution was added and the mixture was extracted with Et_2O (3 x 2.00 mL), the combined organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (1:20 MeOH:CH_2Cl_2) to give morpholine derivative **169** (7.85 mg, 53% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.66 (dt, *J* = 6.8, 1.9 Hz, 1H), 5.03 (qd, *J* = 7.1, 1.4 Hz, 1H), 4.63 (d, *J* = 14.4 Hz, 1H), 4.48 (d, *J* = 14.4 Hz, 1H), 3.78 (s, 3H), 3.76 (d, *J* = 7.1 Hz, 1H), 3.54 (d, *J* = 12.5 Hz, 1H), 3.29 – 3.24 (m, 2H), 2.86 – 2.74 (m, 1H), 2.68 – 2.60 (m, 2H), 2.32 (s, 3H), 2.30 – 2.24 (m, 1H), 2.12 – 1.96 (m, 2H), 1.58 (dd, *J* = 7.1, 1.3 Hz, 3H), 1.55 – 1.49 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.0, 158.9, 148.5, 133.5, 129.5, 129.0, 113.9, 103.5, 77.8, 58.4, 52.2, 49.5, 46.6, 42.4, 37.9, 28.9, 24.3, 11.0; IR (Neat Film NaCl) 3416, 2927, 1663, 1613, 1512, 1454, 1246, 1175, 1034, 817, 732 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{22}H_{29}N_2O_3$ $[M+H]^+$: 369.2173; found: 369.2212.

Typical procedure for aminocyclohexanols 170



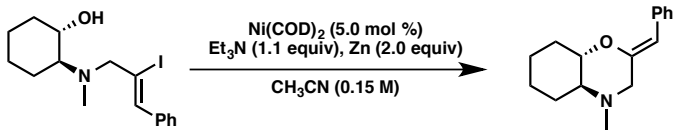
SI-4-4 *SI-4-5* *170*

To a scintillation vial were added cyclohexene oxide **SI-4-4** (5.09 mmol, 1.00 equiv), R^1NH_2 (5.09 mmol, 1.00 equiv), and MeOH (2.50 mL). The reaction mixture was

heated to 80 °C for 12 h. The solvent was evaporated to give the corresponding aminocyclohexanols **SI-4-5**, which were used without further purification.

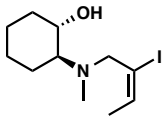
To a solution of aminocyclohexanols **SI-4-5** (5.09 mmol, 1.00 equiv) in MeCN (25.0 mL) were added K_2CO_3 (25.5 mmol, 5.00 equiv) and allyl bromides (5.60 mmol, 1.10 equiv). The reaction mixture was stirred for 12 h at 23 °C. Solids were removed via a filtration through a celite plug and the resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography, using mixture of hexanes and ethyl acetate as eluent to furnish the product **170**.

Representative procedure for cross-coupling of aminocyclohexanols 170



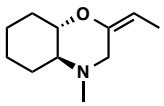
170c ***171c***

Ni-Catalyzed C–O bond formation experiments were performed in a nitrogen-filled glove box. To a solution of aminocyclohexanol **170c** (50.0 mg, 0.135 mmol, 1.00 equiv) in MeCN (0.900 mL) in a scintillation vial were added Et_3N (21.0 μL, 0.149 mmol, 1.10 equiv), Zn powder (17.7 mg, 0.270 mmol, 2.00 equiv), and $Ni(COD)_2$ (1.90 mg, 0.00673 mmol, 0.05 equiv). The reaction mixture was stirred at 23 °C for 24 h. After the reaction was done, the vial was removed from the glove box and uncapped. Solids were removed via a filtration through a celite plug and the resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) to give **171c** (30.7 mg, 93% yield).



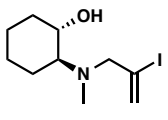
170a

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.41 (q, *J* = 7.1 Hz, 1H), 4.03 (s, 1H), 3.40 (td, *J* = 9.8, 4.5 Hz, 1H), 3.15 (d, *J* = 13.7 Hz, 1H), 3.08 (d, *J* = 13.9 Hz, 1H), 2.26 (ddd, *J* = 14.0, 10.2, 3.6 Hz, 1H), 2.18 (s, 3H), 2.15 – 2.11 (m, 1H), 1.79 (dt, *J* = 8.9, 2.0 Hz, 2H), 1.73 (d, *J* = 7.2 Hz, 3H), 1.31 – 1.17 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.3, 104.4, 69.3, 68.7, 57.3, 35.7, 33.3, 25.6, 24.2, 22.8, 17.0; IR (Neat Film NaCl) 3467, 2930, 2855, 1449, 1282, 1080, 1037 cm^{-1}; HRMS (MM: FAB+) *m/z* calc'd for $C_{11}H_{21}NOI$ $[M+H]^+$: 310.0668; found: 310.0654.



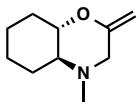
171a

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.02 (qd, *J* = 7.1, 1.6 Hz, 1H), 3.58 (d, *J* = 12.6 Hz, 1H), 3.35 – 3.23 (m, 1H), 2.62 (d, *J* = 12.6 Hz, 1H), 2.29 (s, 3H), 2.09 (dtd, *J* = 12.9, 3.7, 2.0 Hz, 1H), 1.94 (ddt, *J* = 11.9, 4.5, 2.6 Hz, 1H), 1.85 (s, br, 1H), 1.77 – 1.71 (m, 2H), 1.56 (dd, *J* = 7.1, 1.5 Hz, 3H), 1.42 – 1.33 (m, 1H), 1.33 – 1.22 (m, 2H), 1.14 – 1.02 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.9, 103.3, 81.1, 67.4, 53.0, 42.0, 31.4, 28.1, 24.8, 24.4, 11.1; IR (Neat Film NaCl) 2934, 2861, 2779, 1682, 1451, 1192, 1108, 841 cm^{-1}; HRMS (MM: FAB+) *m/z* calc'd for $C_{11}H_{20}NO$ $[M+H]^+$: 182.1545; found: 182.1538.



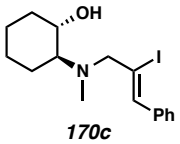
170b

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.28 (q, *J* = 1.4 Hz, 1H), 5.86 (dt, *J* = 0.8, 1.6 Hz, 1H), 3.97 (s, 1H), 3.40 (m, 1H), 3.17 (d, *J* = 13.7 Hz, 1H), 2.96 (d, *J* = 13.7 Hz, 1H), 2.28 (m, 1H), 2.18 (s, 3H), 2.13 (m, 1H), 1.75 (m, 3H), 1.20 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 126.8, 113.7, 69.3, 69.1, 64.8, 35.8, 33.1, 25.4, 24.0, 22.6; IR (neat film NaCl) 3470, 2930, 2855, 2796, 1616, 1448, 1079, 1036 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{10}H_{19}INO$, $[M+H]^+$: 296.0506; found: 296.0499.



171b

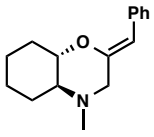
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.40 (s, 1H), 4.16 (s, 1H), 3.36 (ddd, *J* = 2.5, 5.4, 6.7 Hz, 1H), 3.25 (d, *J* = 7.5 Hz, 1H), 2.81 (7.5 Hz, 1H), 2.24 (s, 3H), 2.09 (m, 1H), 1.98 (m, 1H), 1.84 – 1.73 (m, 3H), 1.43 – 1.07 (m, m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1, 91.9, 81.1, 66.8, 57.9, 41.7, 31.3, 28.1, 24.3, 24.3; IR (neat film NaCl) 2929, 2858, 2770, 1747, 1653, 1277, 1229, 1074 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{10}H_{18}NO$, $[M+H]^+$: 168.1383; found: 168.1385.



170c

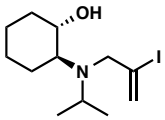
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.50 (m, 2H), 7.40 – 7.29 (m, 3H), 6.97 (s, 1H), 4.04 (s, 1H), 3.52 – 3.41 (m, 2H), 3.27 (dd, *J* = 13.5, 1.1 Hz, 1H), 2.42 – 2.29 (m, 1H), 2.24 (s, 3H), 2.19 – 2.11 (m, 1H), 1.79 (dd, *J* = 6.9, 3.9 Hz, 2H), 1.75 – 1.64 (m, 1H), 1.35 – 1.15 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.4, 135.7, 128.8, 128.3, 128.2, 109.0, 69.5, 69.3, 66.8, 35.8, 33.3, 25.6, 24.2, 22.9; IR (neat film NaCl) 3467,

2930, 2855, 1446, 1079, 1058, 1033, 750, 695 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{16}H_{23}INO$, $[M+H]^+$: 372.0819; found: 372.0859.



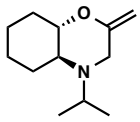
171c

^1H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.53 (m, 2H), 7.32 – 7.25 (m, 2H), 7.17 – 7.11 (m, 1H), 5.44 (d, *J* = 1.7 Hz, 1H), 3.53 (ddd, *J* = 11.5, 9.1, 4.3 Hz, 1H), 3.32 (d, *J* = 12.8 Hz, 1H), 3.00 (dd, *J* = 12.8, 1.6 Hz, 1H), 2.29 (s, 3H), 2.13 (ddtd, *J* = 12.5, 6.2, 4.3, 3.8, 2.1 Hz, 2H), 1.93 (td, *J* = 10.2, 9.1, 3.9 Hz, 1H), 1.79 (ddt, *J* = 13.0, 10.3, 2.9 Hz, 2H), 1.60 – 1.49 (m, 1H), 1.41 – 1.24 (m, 2H), 1.20 – 1.07 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.4, 136.0, 128.5, 128.2, 126.0, 107.5, 80.8, 67.0, 59.2, 41.7, 31.4, 28.3, 24.7, 24.4; IR (neat film NaCl) 2935, 2860, 2774, 1664, 1449, 1342, 1179, 1060, 1032, 694 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{16}H_{22}NO$, $[M+H]^+$: 244.1696; found: 244.1716.



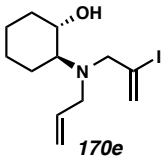
170d

^1H NMR (400 MHz, $CDCl_3$) δ 6.29 (s, 1H), 5.87 (s, 1H), 3.90 (s, 1H), 3.36 – 3.21 (m, 2H), 3.02 (td, *J* = 13.7, 6.6 Hz, 2H), 2.39 (d, *J* = 10.5 Hz, 1H), 2.19 – 2.09 (m, 1H), 1.73 (q, *J* = 10.1 Hz, 3H), 1.35 – 1.17 (m, 4H), 1.14 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 127.2, 116.0, 69.3, 61.7, 57.4, 48.1, 33.2, 28.0, 26.1, 24.4, 22.9, 18.0; IR (neat film NaCl) 2930, 1614, 1173, 1080, 896 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{12}H_{23}NOI$, $[M+H]^+$: 324.0819; found: 324.0845.



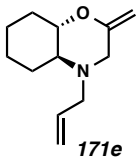
171d

^{1}H NMR (400 MHz, C_6D_6) δ 4.64 (d, *J* = 1.1 Hz, 1H), 4.12 (d, *J* = 1.5 Hz, 1H), 3.48 (ddd, *J* = 11.1, 8.9, 4.3 Hz, 1H), 3.23 (d, *J* = 12.7 Hz, 1H), 3.07 (p, *J* = 6.6 Hz, 1H), 2.89 (dt, *J* = 12.7, 1.4 Hz, 1H), 2.14 (ddd, *J* = 10.8, 8.9, 3.9 Hz, 1H), 2.02 – 1.93 (m, 1H), 1.75 (dq, *J* = 13.6, 2.9, 2.4 Hz, 1H), 1.48 – 1.33 (m, 4H), 0.99 (s, 3H), 0.96 – 0.79 (m, 2H), 0.65 (s, 3H). ^{13}C NMR (101 MHz, C_6D_6) δ 158.4, 89.6, 81.0, 62.1, 46.7, 45.8, 31.8, 28.1, 25.0, 24.4, 21.4, 12.4; IR (neat film NaCl) 2933, 1657, 1450, 1280, 1175, 1075, 800 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{12}H_{22}NO$, $[M+H]^+$: 196.1696; found: 196.1697.



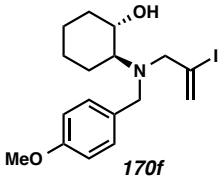
170e

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.29 (d, *J* = 1.8 Hz, 1H), 5.92 – 5.81 (m, 2H), 5.23 – 5.10 (m, 2H), 3.83 (s, 1H), 3.41 (td, *J* = 9.9, 4.5 Hz, 1H), 3.34 (d, *J* = 14.2 Hz, 1H), 3.31 – 3.23 (m, 1H), 2.94 (dd, *J* = 14.1, 8.4 Hz, 1H), 2.88 (d, *J* = 14.2 Hz, 1H), 2.41 (ddd, *J* = 12.7, 9.9, 3.4 Hz, 1H), 2.13 (ddq, *J* = 12.2, 4.6, 2.0 Hz, 1H), 1.85 – 1.74 (m, 2H), 1.71 – 1.68 (m, 1H), 1.32 – 1.16 (m, 3H), 1.15 – 1.03 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.4, 127.6, 117.9, 113.9, 69.1, 64.9, 60.4, 52.4, 33.2, 25.7, 24.2, 23.5; IR (neat film NaCl) 2930, 2856, 1615, 1450, 1157, 1078, 917 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{12}H_{21}NIO$, $[M+H]^+$: 322.0662; found: 322.0668.



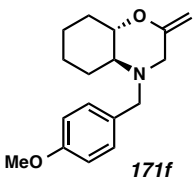
171e

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (dddd, *J* = 17.1, 10.2, 8.0, 5.4 Hz, 1H), 5.24 – 5.16 (m, 2H), 4.38 (dt, *J* = 1.3, 0.7 Hz, 1H), 4.13 (dd, *J* = 1.6, 0.7 Hz, 1H), 3.48 (ddt, *J* = 13.6, 5.4, 1.6 Hz, 1H), 3.45 – 3.40 (m, 1H), 3.35 (d, *J* = 12.9 Hz, 1H), 2.88 – 2.79 (m, 2H), 2.17 – 2.04 (m, 2H), 1.99 (dddd, *J* = 10.2, 4.8, 3.9, 2.4 Hz, 1H), 1.79 – 1.69 (m, 2H), 1.46 – 1.37 (m, 1H), 1.35 – 1.21 (m, 2H), 1.12 (q, *J* = 12.3, 11.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.4, 134.3, 118.8, 91.6, 80.8, 64.6, 56.0, 53.7, 31.5, 28.2, 24.8, 24.3; IR (neat film NaCl) 2935, 2862, 1657, 1280, 1075, 839 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{12}H_{20}NO$, $[M+H]^+$: 194.1539; found: 194.1542.



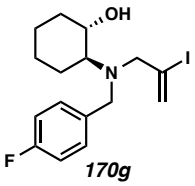
170f

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.32 (d, *J* = 1.7 Hz, 1H), 5.90 (t, *J* = 1.4 Hz, 1H), 3.80 (s, 3H), 3.81 – 3.74 (m, 2H), 3.44 (td, *J* = 9.8, 4.6 Hz, 1H), 3.36 (d, *J* = 13.9 Hz, 1H), 3.28 (d, *J* = 13.2 Hz, 1H), 2.92 (d, *J* = 14.0 Hz, 1H), 2.42 – 2.29 (m, 1H), 2.13 – 2.04 (m, 1H), 1.90 – 1.81 (m, 1H), 1.75 (ddd, *J* = 6.7, 4.4, 2.3 Hz, 1H), 1.70 – 1.63 (m, 1H), 1.25 – 1.04 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.0, 130.6, 130.5, 128.1, 113.9, 113.5, 68.9, 63.6, 60.5, 55.4, 52.8, 33.3, 25.6, 24.2, 22.6; IR (neat film NaCl) 3483, 2931, 2855, 1612, 1511, 1247, 1036, 813 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{17}H_{25}INO_2$, $[M+H]^+$: 402.0924; found: 402.0934.



171f

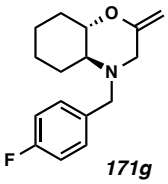
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.3 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 4.33 (s, 1H), 4.09 – 3.96 (m, 2H), 3.81 (s, 3H), 3.51 (s, br, 1H), 3.19 (d, *J* = 13.0 Hz, 1H), 3.09 (d, *J* = 12.9 Hz, 1H), 2.71 (d, *J* = 13.0 Hz, 1H), 2.21 (d, *J* = 12.9 Hz, 1H), 2.13 (s, br, 1H), 2.06 – 1.96 (m, 1H), 1.84 – 1.72 (m, 2H), 1.50 – 1.36 (m, 1H), 1.32 (qd, *J* = 11.1, 9.7, 5.6 Hz, 2H), 1.22 (d, *J* = 22.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9, 156.5, 130.4, 130.2, 113.8, 91.1, 80.4, 65.2, 56.5, 55.4, 53.4, 31.6, 28.7, 24.8, 24.4; IR (neat film NaCl) 2935, 2861, 1733, 1674, 1611, 1511, 1246, 1036, 843 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{17}H_{24}NO_2$, $[M+H]^+$: 274.1802; found: 274.1820.



170g

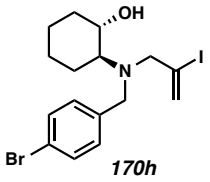
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 8.4, 5.6 Hz, 2H), 7.01 (t, *J* = 8.7 Hz, 2H), 6.33 (s, 1H), 5.91 (t, *J* = 1.4 Hz, 1H), 3.80 (d, *J* = 13.3 Hz, 1H), 3.73 (s, br, 1H), 3.45 (td, *J* = 9.7, 4.6 Hz, 1H), 3.35 (t, *J* = 12.6 Hz, 2H), 2.95 (d, *J* = 13.9 Hz, 1H), 2.33 (d, *J* = 10.4 Hz, 1H), 2.14 – 2.04 (m, 1H), 1.92 – 1.83 (m, 1H), 1.81 – 1.72 (m, 1H), 1.67 (dt, *J* = 7.8, 2.8 Hz, 1H), 1.25 – 1.06 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.3 (d, *J* = 245.2 Hz), 134.2, 131.1 (d, *J* = 8.0 Hz), 128.4, 115.5 (d, *J* = 21.3 Hz), 113.1, 68.9, 63.8, 60.6, 52.7, 33.3, 25.5, 24.2, 22.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ -115.5; IR (neat film NaCl) 3485, 2930, 2856, 1602, 1508, 1221, 1152, 1073, 818 cm^{-1};

HRMS (MM: ESI-APCI+) m/z calc'd for $C_{16}H_{22}FNOI$, $[M+H]^+$: 390.0725; found: 390.0732.



171g

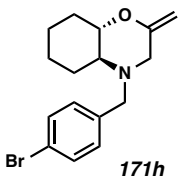
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.25 (m, 2H), 7.08 – 6.93 (m, 2H), 4.34 (s, 1H), 4.04 (d, *J* = 13.1 Hz, 1H), 3.99 (d, *J* = 1.5 Hz, 1H), 3.50 (tt, *J* = 11.8, 10.9, 4.1 Hz, 2H), 3.16 (d, *J* = 13.0 Hz, 1H), 3.08 (d, *J* = 13.2 Hz, 1H), 2.72 (d, *J* = 12.9 Hz, 1H), 2.24 – 2.05 (m, 2H), 2.07 – 1.94 (m, 1H), 1.87 – 1.66 (m, 2H), 1.53 – 1.35 (m, 1H), 1.38 – 1.24 (m, 1H), 1.24 – 1.13 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.1 (d, *J* = 244.7 Hz), 156.3, 134.3, 130.1 (d, *J* = 6.1 Hz), 115.3 (d, *J* = 20.9 Hz), 91.2, 80.5, 65.3, 56.4, 53.6, 31.6, 28.8, 24.8, 24.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ -116.0; IR (neat film NaCl) 2936, 2862, 1736, 1673, 1604, 1508, 1222, 1075, 821 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{16}H_{21}FNO$, $[M+H]^+$: 262.1602; found: 262.1629.



170h

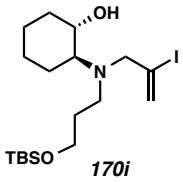
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.7 Hz, 2H), 7.27 (d, *J* = 7.7 Hz, 2H), 6.33 (s, br, 1H), 5.91 (t, *J* = 1.6 Hz, 1H), 3.78 (d, *J* = 13.3 Hz, 1H), 3.71 (s, br, 1H), 3.53 – 3.41 (m, 1H), 3.42 – 3.26 (m, 2H), 2.95 (d, *J* = 14.0 Hz, 1H), 2.33 (s, br, 1H), 2.08 (dd, *J* = 9.6, 4.3 Hz, 1H), 1.94 – 1.54 (m, 3H), 1.27 – 1.03 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.5, 131.7, 131.2, 128.6, 121.4, 112.9, 69.0, 63.9, 60.6, 52.9, 33.3, 25.5, 24.2, 22.6; IR (neat film NaCl) 3486, 2930, 2855, 1615, 1486, 1450, 1403, 1152,

1071, 1011, 799 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{16}H_{22}BrNOI$, $[M+H]^+$: 449.9924; found: 449.9937.



171h

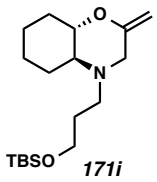
^1H NMR (500 MHz, CD_2Cl_2) δ 7.44 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.3 Hz, 2H), 4.24 (d, *J* = 1.1 Hz, 1H), 4.02 (d, *J* = 13.4 Hz, 1H), 3.93 (d, *J* = 1.5 Hz, 1H), 3.44 (ddd, *J* = 11.2, 8.7, 4.2 Hz, 1H), 3.13 (d, *J* = 12.9 Hz, 1H), 3.02 (d, *J* = 13.5 Hz, 1H), 2.69 (dt, *J* = 12.9, 1.5 Hz, 1H), 2.18 – 2.07 (m, 2H), 2.02 – 1.91 (m, 1H), 1.75 (tdd, *J* = 10.4, 5.5, 2.5 Hz, 2H), 1.47 – 1.34 (m, 1H), 1.36 – 1.22 (m, 2H), 1.19 – 1.06 (m, 1H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 157.1, 138.9, 131.8, 131.2, 121.0, 90.7, 81.0, 65.8, 56.9, 54.2, 31.9, 29.1, 25.2, 24.7; IR (neat film NaCl) 2935, 2861, 1654, 1486, 1280, 1074, 1012, 843, 802 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{16}H_{21}BrNO$, $[M+H]^+$: 322.0801; found: 322.0817.



170i

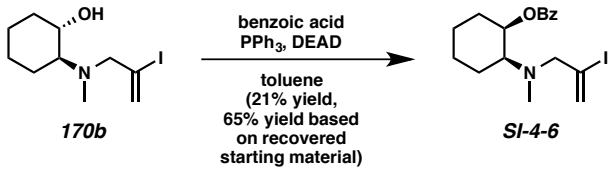
^1H NMR (500 MHz, $CDCl_3$) δ 6.28 (s, 1H), 5.84 (s, 1H), 3.83 (s, 1H), 3.66 (td, *J* = 6.2, 2.2 Hz, 2H), 3.38 (td, *J* = 9.9, 4.4 Hz, 1H), 3.29 (d, *J* = 14.1 Hz, 1H), 2.91 (d, *J* = 14.2 Hz, 1H), 2.65 (dt, *J* = 13.0, 8.0 Hz, 1H), 2.43 (ddd, *J* = 13.1, 7.4, 5.8 Hz, 1H), 2.34 (ddd, *J* = 12.6, 9.8, 3.3 Hz, 1H), 2.17 – 2.08 (m, 1H), 1.82 – 1.72 (m, 2H), 1.71 (dt, *J* = 8.4, 6.0 Hz, 3H), 1.32 – 1.14 (m, 3H), 1.10 (tt, *J* = 12.2, 5.9 Hz, 1H), 0.89 (d,

J = 0.9 Hz, 9H), 0.05 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 127.3, 114.2, 69.1, 65.6, 61.6, 61.4, 46.1, 33.3, 31.9, 26.1, 25.7, 24.3, 23.1, 18.4, -5.11, -5.13; IR (neat film NaCl) 3489, 2929, 2856, 1255, 1097, 835, 775 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{18}H_{37}INO_2Si$, $[M+H]^+$: 454.1633; found: 454.1658.



171i

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.38 (s, 1H), 4.13 (s, 1H), 3.63 (td, *J* = 6.2, 2.2 Hz, 2H), 3.47 – 3.31 (m, 2H), 2.94 – 2.79 (m, 2H), 2.34 (s, br, 1H), 2.15 – 2.04 (m, 2H), 1.98 (ddq, *J* = 11.8, 4.4, 2.4, 1.9 Hz, 1H), 1.79 – 1.59 (m, 5H), 1.46 – 1.21 (m, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.5, 91.4, 80.9, 64.6, 61.4, 53.8, 49.3, 31.5, 28.9, 28.3, 26.1, 24.8, 24.3, 18.4, -5.15, -5.17; IR (neat film NaCl) 2931, 2857, 1739, 1674, 1463, 1256, 1094, 838, 776 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{18}H_{36}NO_2Si$, $[M+H]^+$: 326.2510; found: 326.2544.

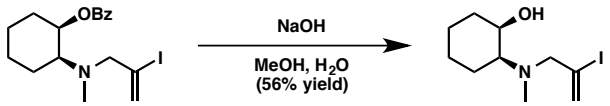


170b ***SI-4-6***

A solution of cyclohexanol **170b** (500 mg, 1.69 mmol, 1.00 equiv) in toluene (1.20 mL) was added to a cooled solution of PPh_3 (532 mg, 2.03 mmol, 1.20 equiv) and benzoic acid (248 mg, 2.03 mmol, 1.20 equiv) in toluene (8.45 mL) at –40 °C. Then, DEAD in toluene (40 wt% in toluene, 0.92 mL, 1.20 equiv) was added dropwise to a solution over 20 min at –40 °C. After stirring for 1.5 h at –40 °C, the solution was warmed to 23 °C. After being stirred for 18 h, saturated $NaHCO_3$ aqueous solution

was added and the mixture was extracted with EtOAc (3 x 7.00 mL). The combined organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (1:20 EtOAc:hexanes) to give benzoate **SI-4-6** (142 mg, 21% yield, 65% yield based on recovered starting material).

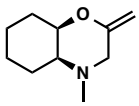
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.1 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 2H), 6.25 (s, 1H), 5.73 (s, 1H), 5.10 (td, *J* = 10.4, 4.6 Hz, 1H), 3.29 (d, *J* = 15.1 Hz, 1H), 3.22 (d, *J* = 15.1 Hz, 1H), 2.79 – 2.69 (m, 1H), 2.25 (s, 3H), 2.19 – 2.11 (m, 1H), 1.92 (d, *J* = 13.1 Hz, 1H), 1.83 – 1.72 (m, 2H), 1.40 (dddd, *J* = 17.5, 10.7, 8.0, 3.7 Hz, 2H), 1.35 – 1.23 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.0, 132.9, 131.0, 129.9, 128.4, 125.5, 113.4, 73.5, 67.3, 65.8, 36.2, 32.2, 27.4, 25.3, 24.5; IR (Neat Film NaCl) 2934, 2858, 1714, 1450, 1317, 1273, 1175, 1106, 710 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{17}H_{23}INO_2$ $[M+H]^+$: 400.0768; found: 400.0769.



SI-4-6 *170j*

A solution of benzoate **SI-4-6** (140 mg, 0.351 mmol, 1.00 equiv) in MeOH (1.80 mL) and H_2O (0.20 mL) was treated with NaOH (28 mg, 0.701 mmol, 2.00 equiv) at 60 °C. After 1 h and 45 min, the solution was poured into H_2O and the mixture was extracted with CH_2Cl_2 (3 x 3.00 mL). The combined organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (1:8 EtOAc:hexanes) to give cyclohexanol **170j** (58 mg, 56% yield).

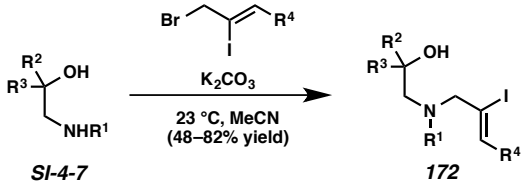
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.28 (q, *J* = 1.4 Hz, 1H), 5.86 (dt, *J* = 1.6, 0.8 Hz, 1H), 3.96 (s, 1H), 3.40 (td, *J* = 9.9, 4.5 Hz, 1H), 3.17 (d, *J* = 13.8 Hz, 1H), 2.95 (d, *J* = 13.8 Hz, 1H), 2.28 (ddd, *J* = 11.4, 9.7, 3.5 Hz, 1H), 2.18 (s, 3H), 2.18 – 2.09 (m, 1H), 1.83 – 1.65 (m, 3H), 1.35 – 1.07 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 127.0, 113.8, 69.4, 69.3, 65.0, 35.9, 33.3, 25.6, 24.2, 22.8; IR (Neat Film NaCl) 3468, 2930, 2855, 2796, 1615, 1449, 1282, 1080, 1036, 901 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{10}H_{19}INO$ $[M+H]^+$: 296.0506; found: 296.0528.



171j

^{1}H NMR (400 MHz, CD_2Cl_2) δ 4.28 (dd, *J* = 1.4, 0.7 Hz, 1H), 4.09 (dd, *J* = 1.7, 0.5 Hz, 1H), 3.31 (ddd, *J* = 11.2, 9.0, 4.2 Hz, 1H), 3.21 (d, *J* = 12.7 Hz, 1H), 2.75 (dt, *J* = 12.7, 1.6 Hz, 1H), 2.18 (s, 3H), 2.12 – 2.01 (m, 1H), 1.90 (dtd, *J* = 13.3, 4.7, 2.7 Hz, 1H), 1.81 – 1.66 (m, 3H), 1.43 – 1.23 (m, 3H), 1.03 (tdd, *J* = 13.0, 11.2, 3.7 Hz, 1H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 157.3, 91.0, 81.4, 67.2, 58.2, 41.9, 31.7, 28.5, 25.1, 24.8; IR (Neat Film NaCl) 2937, 2862, 2770, 1654, 1451, 1339, 1278, 1161, 1075, 1042, 900, 836 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{10}H_{18}NO$ $[M+H]^+$: 168.1383; found: 168.1396.

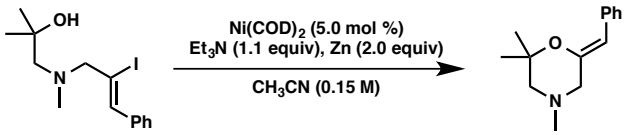
Typical procedure for linear aminoalcohols 172



SI-4-7 ***172***

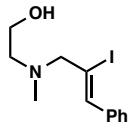
To a solution of aminoalcohols **SI-4-7** (1.12 mmol, 1.00 equiv) in MeCN (5.60 mL) were added K_2CO_3 (11.2 mmol, 10.0 equiv) and allyl bromides (1.23 mmol, 1.10 equiv). The reaction mixture was stirred for 12 h at 23 °C. Solids were removed via a filtration through a celite plug and the resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography, using mixture of hexanes and ethyl acetate as eluent to give the product **172**.

Representative procedure for cross-coupling of linear aminoalcohols 172



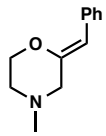
172c ***173c***

Ni-Catalyzed C–O bond formation experiments were performed in a nitrogen-filled glove box. To a solution of aminoalcohol **172c** (50.0 mg, 0.145 mmol, 1.00 equiv) in MeCN (0.97 mL) in a scintillation vial were added Et_3N (22.0 μL, 0.160 mmol, 1.10 equiv), Zn powder (19.0 mg, 0.290 mmol, 2.00 equiv), and $Ni(COD)_2$ (2.00 mg, 0.00724 mmol, 0.05 equiv). The reaction mixture was stirred at 23 °C for 24 h. After the reaction was done, the vial was removed from the glovebox and uncapped. Solids were removed via a filtration through a celite plug and the resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography, using a mixture of hexanes and ethyl acetate as eluent to furnish the product **173c** (30.0 mg, 95% yield).



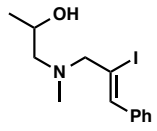
172a

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (m, 2H), 7.36 (m, 3H), 6.98 (s, 1H), 3.65 (t, *J* = 5.4 Hz, 2H), 3.36 (s, 2H), 2.95 (br, 1H), 2.66 (t, *J* = 5.5 Hz, 2H), 2.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.2, 136.1, 128.7, 128.1, 128.0, 107.1, 70.4, 58.5, 57.8, 40.7; IR (neat film NaCl) 3442, 2946, 2840, 2792, 1490, 1445, 1083, 1066, 1046, 748, 694 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{12}H_{17}INO$, $[M+H]^+$: 318.0349; found: 318.0344.



173a

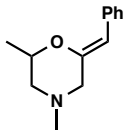
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (m, 2H), 7.28 (m, 2H), 7.14 (m, 1H), 5.45 (s, 1H), 4.06 (m, 2H), 3.03 (s, 2H), 2.59 (m, 2H), 2.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.6, 135.6, 128.4, 128.1, 125.9, 107.9, 67.4, 58.3, 54.1, 46.1; IR (neat film NaCl) 2939. 2790, 1738, 1668, 1452, 1339, 1170, 1051, 695; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{12}H_{16}NO$, $[M+H]^+$: 190.1226; found: 190.1228.



172b

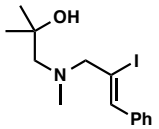
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.50 (m, 2H), 7.41 – 7.30 (m, 3H), 6.98 (s, 1H), 3.90 (dqd, *J* = 9.4, 6.1, 3.0 Hz, 1H), 3.75 – 3.53 (m, 1H), 3.47 (d, *J* = 13.5 Hz, 1H), 3.29 (d, *J* = 13.5 Hz, 1H), 2.45 (dd, *J* = 12.3, 3.1 Hz, 1H), 2.41 – 2.36 (m, 1H), 2.32 (s, 3H), 1.16 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.4, 136.4, 128.8, 128.3, 128.3, 128.2, 107.1, 70.8, 64.6, 63.3, 41.3, 19.9; IR (neat film NaCl) 3459, 3054, 3023, 2968, 2930, 2843, 2795, 1598, 1491, 1446, 1408, 1361, 1324, 1291,

1209, 1161, 1135, 1065, 1029, 935, 841, 750, 695 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{13}H_{19}NIO$, $[M+H]^+$: 332.0506; found: 332.0519.



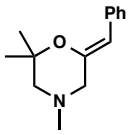
173b

^1H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.56 (m, 2H), 7.33 – 7.26 (m, 2H), 7.19 – 7.10 (m, 1H), 5.46 (d, *J* = 1.4 Hz, 1H), 4.06 (dqd, *J* = 9.9, 6.3, 2.6 Hz, 1H), 3.20 (dd, *J* = 12.5, 1.7 Hz, 1H), 2.85 – 2.72 (m, 2H), 2.31 (s, 3H), 2.06 (dd, *J* = 11.7, 9.8 Hz, 1H), 1.36 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.2, 136.0, 128.6, 128.2, 126.0, 107.8, 73.4, 60.9, 58.0, 46.1, 19.2; IR (neat film NaCl) 2973, 2936, 2788, 1666, 1448, 1328, 1154, 1070, 975, 755, 694 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{13}H_{18}NO$, $[M+H]^+$: 204.1383; found: 204.1386.



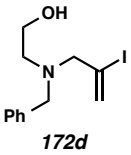
172c

^1H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.48 (m, 2H), 7.33 (s, 3H), 6.99 (s, 1H), 3.46 (s, 2H), 3.26 (s, br, 1H), 2.51 (s, 2H), 2.37 (s, 3H), 1.23 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.5, 135.8, 129.2, 128.9, 128.2, 108.3, 73.0, 70.9, 68.1, 44.0, 28.0; IR (neat film NaCl) 2969, 2786, 2360, 1446, 1356, 1121, 1031, 970, 749, 695 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{14}H_{21}NIO$, $[M+H]^+$: 346.0662; found: 346.0664.



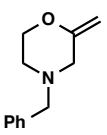
173c

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.59 (m, 2H), 7.29 – 7.25 (m, 2H), 7.17 – 7.09 (m, 1H), 5.47 (s, 1H), 2.94 (s, 2H), 2.38 (s, 2H), 2.28 (s, 3H), 1.39 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.2, 136.3, 128.3, 128.2, 125.8, 108.7, 76.8, 64.7, 58.3, 46.4, 26.3; IR (neat film NaCl) 2974, 2766, 1663, 1449, 1368, 1346, 1254, 1207, 1152, 1110, 968, 754, 694 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{14}H_{20}NO$, $[M+H]^+$: 218.1539; found: 218.1577.



172d

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.25 (m, 5H), 6.33 (q, *J* = 1.4 Hz, 1H), 5.92 (m, 1H), 3.63 (s, 2H), 3.56 (q, *J* = 5.4 Hz, 2H), 3.16 (s, 2H), 2.70 (t, *J* = 5.7 Hz, 1H), 2.65 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 129.3, 128.4, 127.9, 127.4, 111.9, 64.8, 58.5, 57.5, 54.1; IR (neat film NaCl) 3435, 3024, 2808, 1616, 1493, 1452, 1257, 1151, 1027, 904, 739, 698 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{12}H_{17}INO$, $[M+H]^+$: 318.0349; found: 318.0356.

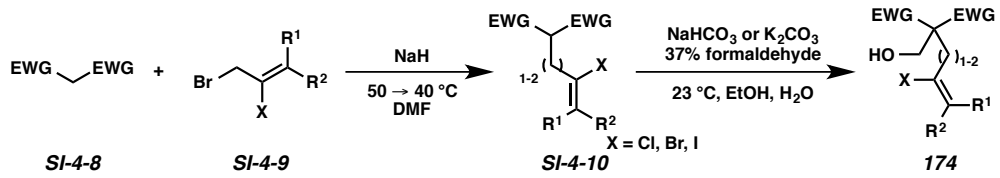


173d

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.24 (m, 5H), 4.39 (s, 1H), 4.11 (s, 1H), 3.90 (m, 2H), 3.50 (s, 2H), 2.98 (s, 2H), 2.52 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 137.4, 129.3, 128.5, 127.4, 92.2, 67.9, 63.2, 55.3, 52.1; IR (neat film NaCl)

2875, 2807, 1653, 1453, 1313, 1278, 1125, 1079, 1067, 851, 699 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{12}H_{16}NO$, $[M+H]^+$: 190.1226; found: 190.1229.

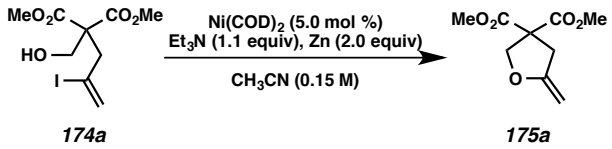
Typical procedure for malonate substrates 174



To a suspension of NaH (60% dispersion in mineral oil, 4.16 mmol, 1.10 equiv) in DMF (19.0 mL) at 0 °C was added malonate **SI-4-8** (3.78 mmol, 1.00 equiv) in portions. The reaction mixture was stirred at 50 °C for 1 h. The solution was cooled to 0 °C and allyl bromide (3.78 mmol, 1.00 equiv) in DMF (2 mL) was added in portions over 5 min. Then, the mixture was stirred at 40 °C for 1 h. The reaction was quenched by sat. NH_4Cl and the aqueous phase was extracted with Et_2O (3 x 10.0 mL). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:20 EtOAc:hexanes) on silica gel to give vinyl halide **SI-4-10**.

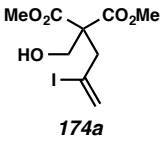
To a solution of vinyl halide **SI-4-10** (0.74 mmol, 1.00 equiv) in EtOH (0.50 mL) and H_2O (0.25 mL) were added solid $NaHCO_3$ or K_2CO_3 (0.15 mmol, 0.20 equiv) and formaldehyde (37wt.% in H_2O, 0.89 mmol, 1.20 equiv). The reaction mixture was stirred at 23 °C for 24 h. Then, water (0.40 mL) was added and the aqueous phase was extracted with EtOAc (3 x 1.00 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography, using a mixture of hexanes and ethyl acetate as eluent to furnish the product **174**.

Representative procedure for cross-coupling of malonates 174



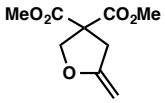
174a *175a*

Ni-Catalyzed C–O bond formation experiments were performed in a nitrogen-filled glove box. To a solution of vinyl iodide **174a** (83.9 mg, 0.256 mmol, 1.00 equiv) in MeCN (1.71 mL) in a scintillation vial were added Et_3N (39.0 μL, 0.282 mmol, 1.10 equiv), Zn powder (33.0 mg, 0.512 mmol, 2.00 equiv), and $Ni(COD)_2$ (3.50 mg, 0.013 mmol, 0.05 equiv). The reaction mixture was stirred at 23 °C for 1 h. After the reaction was done, the vial was removed from the glovebox and uncapped. Solids were removed via a filtration through a celite plug and the resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography (1:4 EtOAc:hexanes) to furnish the product **175a** (44.5 mg, 87% yield).



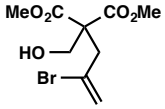
174a

^{1}H NMR (500 MHz, C_6D_6) δ 5.79 (q, *J* = 1.2 Hz, 1H), 5.61 (d, *J* = 1.4 Hz, 1H), 4.09 (d, *J* = 5.8 Hz, 2H), 3.33 (s, 6H), 3.32 (d, *J* = 1.1 Hz, 2H); ^{13}C NMR (126 MHz, C_6D_6) δ 169.9, 131.5, 101.2, 63.3, 59.3, 52.4, 45.4; IR (Neat Film NaCl) 3520, 2952, 1731, 1435, 1210, 1033 cm^{-1}; HRMS (MM: FAB+) *m/z* calc'd for $C_9H_{14}IO_5$ $[M+H]^+$: 328.9886; found: 328.9891.



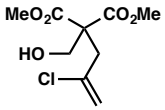
175a

^{1}H NMR (500 MHz, C_6D_6) δ 4.53 (q, *J* = 1.9 Hz, 1H), 4.44 (s, 2H), 3.91 (q, *J* = 1.7 Hz, 1H), 3.16 (s, 6H), 3.09 (t, *J* = 1.7 Hz, 2H); ^{13}C NMR (126 MHz, C_6D_6) δ 169.2, 160.2, 81.8, 74.3, 59.8, 52.6, 37.0; IR (Neat Film NaCl) 2957, 2358, 2340, 1737, 1436, 1280, 1046 cm^{-1}; HRMS (MM: ESI-APCI +) *m/z* calc'd for $C_9H_{13}O_5$ $[M+H]^+$: 201.0757; found: 201.0765.



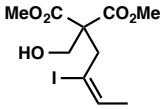
174b

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74 (dt, *J* = 1.7, 0.9 Hz, 1H), 5.59 (d, *J* = 1.7 Hz, 1H), 4.09 (s, 2H), 3.79 (s, 6H), 3.25 (d, *J* = 0.9 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.4, 126.6, 122.4, 63.7, 59.0, 53.1, 42.4; IR (Neat Film NaCl) 2953, 1728, 1626, 1435, 1299, 1208, 1032, 902, 857 cm^{-1}; HRMS (MM: FAB+) *m/z* calc'd for $C_9H_{14}BrO_5$ $[M+H]^+$: 281.0024; found: 281.0036.



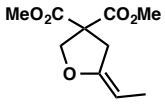
174c

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.32 (d, *J* = 1.3 Hz, 1H), 5.30 – 5.28 (m, 1H), 4.07 (s, 2H), 3.78 (s, 6H), 3.13 (d, *J* = 0.8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 136.6, 117.7, 63.8, 58.7, 53.0, 40.6; IR (Neat Film NaCl) 2955, 1735, 1632, 1437, 1212, 1035, 898 cm^{-1}; HRMS (MM: FAB +) *m/z* calc'd for $C_9H_{14}O_5Cl$ $[M+H]^+$: 237.0530; found: 237.0540.



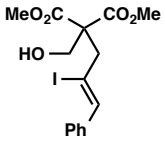
174d

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.50 (qt, *J* = 7.2, 0.8 Hz, 1H), 4.04 (d, *J* = 6.6 Hz, 2H), 3.80 (s, 6H), 3.30 (s, br, 2H), 2.36 (t, *J* = 6.7 Hz, 1H), 1.70 (dt, *J* = 7.2, 0.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 142.1, 91.5, 63.6, 59.2, 53.1, 38.7, 17.2; IR (Neat Film NaCl) 2952, 1733, 1436, 1299, 1223, 1040 cm^{-1}; HRMS (MM: FAB +) *m/z* calc'd for $C_{10}H_{16}O_5I$ $[M+H]^+$: 343.0043; found: 343.0048.



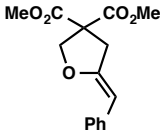
175d

^{1}H NMR (400 MHz, C_6D_6) δ 4.97 (qt, *J* = 7.0, 2.2 Hz, 1H), 4.44 (s, 2H), 3.18 (s, 6H), 3.11 (dq, *J* = 2.8, 1.5 Hz, 2H), 1.40 (dt, *J* = 7.1, 1.4 Hz, 3H); ^{13}C NMR (101 MHz, C_6D_6) δ 169.6, 153.8, 92.2, 73.6, 59.7, 52.6, 34.2, 12.2; IR (Neat Film NaCl) 2956, 1740, 1437, 1275, 1169, 1070, 803 cm^{-1}; HRMS (MM: FAB +) *m/z* calc'd for $C_{10}H_{14}O_5$ $[M]^{+\bullet}$: 214.0841; found: 214.0836.



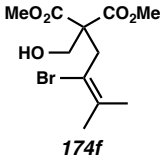
174e

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.28 (m, 5H), 6.88 (s, 1H), 4.15 (s, 2H), 3.81 (s, 6H), 3.57 (d, *J* = 0.9 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 140.1, 138.2, 128.7, 128.3, 128.3, 96.5, 63.6, 59.9, 53.1, 46.9; IR (Neat Film NaCl) 2951, 1727, 1437, 1215, 1032, 696 cm^{-1}; HRMS (MM: ESI-APCI +) *m/z* calc'd for $C_{15}H_{18}O_5I$ $[M+H]^+$: 405.0193; found: 405.0195.



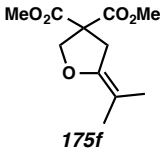
175e

^{1}H NMR (400 MHz, C_6D_6) δ 7.75 – 7.70 (m, 2H), 7.25 (t, *J* = 7.8 Hz, 2H), 7.05 (ddt, *J* = 8.6, 7.2, 1.2 Hz, 1H), 5.21 – 5.18 (m, 1H), 4.54 (s, 2H), 3.20 (d, *J* = 1.6 Hz, 2H), 3.16 (s, 6H); ^{13}C NMR (101 MHz, C_6D_6) δ 168.8, 153.7, 136.4, 128.2, 127.8, 125.3, 99.4, 75.2, 58.5, 52.3, 38.3; IR (Neat Film NaCl) 2953, 1738, 1678, 1435, 1279, 1210, 1028, 695 cm^{-1}; HRMS (MM: EI +) *m/z* calc'd for $C_{15}H_{16}O_5$ $[M]^{+\bullet}$: 276.0998; found: 276.1012.



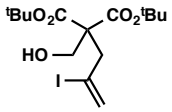
174f

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.02 (s, 2H), 3.78 (s, 6H), 3.37 (s, 2H), 1.88 (d, *J* = 0.9 Hz, 3H), 1.83 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 136.4, 114.1, 63.7, 59.3, 53.0, 38.8, 25.9, 21.2; IR (Neat Film NaCl) 2952, 1734, 1437, 1209, 1043 cm^{-1}; HRMS (MM: FAB +) *m/z* calc'd for $C_{11}H_{18}O_5Br$ $[M+H]^+$: 309.0338; found: 309.0325.



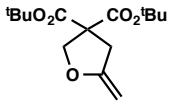
175f

^{1}H NMR (500 MHz, C_6D_6) δ 4.12 (d, *J* = 6.0 Hz, 2H), 3.57 (s, 2H), 3.38 (s, 6H), 1.66 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (126 MHz, C_6D_6) δ 170.6, 136.2, 115.0, 63.6, 59.5, 52.3, 39.0, 25.6, 20.8; IR (Neat Film NaCl) 2952, 1731, 1437, 1301, 1209, 1043 cm^{-1}; HRMS (MM: FAB +) *m/z* calc'd for $C_{11}H_{17}O_5$ $[M+H]^+$: 229.1076; found: 229.1074.



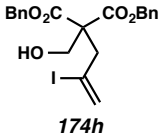
174g

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.18 (q, *J* = 1.3 Hz, 1H), 5.91 (d, *J* = 1.5 Hz, 1H), 4.06 (d, *J* = 3.6 Hz, 2H), 3.20 (d, *J* = 1.1 Hz, 2H), 2.32 (s, 1H), 1.50 (s, 18H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.1, 130.9, 101.6, 82.8, 63.9, 60.7, 45.4, 28.1; IR (Neat Film NaCl) 2978, 1728, 1369, 1256, 1148, 1020, 842 cm^{-1}; HRMS (MM: FAB +) *m/z* calc'd for $C_{15}H_{26}O_5I$ $[M+H]^+$: 413.0825; found: 413.0821.



175g

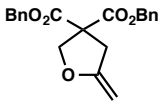
^{1}H NMR (500 MHz, C_6D_6) δ 4.54 (q, *J* = 1.8 Hz, 1H), 4.51 (s, 2H), 3.94 (q, *J* = 1.6 Hz, 1H), 3.14 (t, *J* = 1.7 Hz, 2H), 1.27 (s, 18H); ^{13}C NMR (126 MHz, C_6D_6) δ 168.3, 160.9, 81.8, 81.3, 74.5, 61.2, 37.0, 27.7; IR (Neat Film NaCl) 2979, 1732, 1370, 1146, 1050, 844 cm^{-1}; HRMS (MM: FAB +) *m/z* calc'd for $C_{15}H_{25}O_5$ $[M+H]^+$: 285.1702; found: 285.1693.



174h

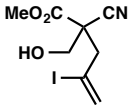
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.29 (m, 6H), 7.29 – 7.26 (m, 4H), 6.12 (q, *J* = 1.1 Hz, 1H), 5.87 (d, *J* = 1.6 Hz, 1H), 5.17 (d, *J* = 3.2 Hz, 4H), 4.13 (s, 2H), 3.29 (d, *J* = 1.1 Hz, 2H), 2.27 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.6, 135.1, 131.8, 128.7, 128.6, 128.4, 100.3, 67.8, 63.6, 59.5, 45.4; IR (Neat Film NaCl) 2952, 1725, 1455,

1214, 695 cm^{-1}; HRMS (MM: ESI-APCI +) *m/z* calc'd for $C_{21}H_{22}O_5I$ $[M+H]^+$: 481.0506; found: 481.0509.



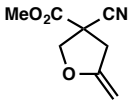
175h

^1H NMR (600 MHz, C_6D_6) δ 7.10 – 6.90 (m, 10H), 4.83 (d, *J* = 8.0 Hz, 4H), 4.50 (q, *J* = 1.8 Hz, 1H), 4.46 (s, 2H), 3.87 (q, *J* = 1.7 Hz, 1H), 3.11 (t, *J* = 1.7 Hz, 2H); ^{13}C NMR (151 MHz, C_6D_6) δ 168.7, 148.2, 135.6, 128.7, 128.5, 128.3, 81.9, 74.3, 67.7, 55.8, 37.0; IR (Neat Film NaCl) 2915, 1732, 1455, 1243, 1045, 901, 695 cm^{-1}; HRMS (MM: ESI-APCI +) *m/z* calc'd for $C_{21}H_{21}O_5$ $[M+H]^+$: 353.1384; found: 353.1394.



174i

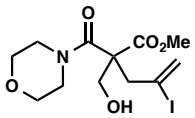
^1H NMR (500 MHz, $CDCl_3$) δ 6.35 (dt, *J* = 2.2, 1.1 Hz, 1H), 6.05 (d, *J* = 2.1 Hz, 1H), 4.04 (dd, *J* = 11.1, 7.6 Hz, 1H), 3.98 (dd, *J* = 11.1, 6.5 Hz, 1H), 3.90 (s, 3H), 3.13 (dd, *J* = 14.9, 1.1 Hz, 1H), 3.05 (dd, *J* = 14.9, 1.1 Hz, 1H), 2.45 (dd, *J* = 7.6, 6.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.6, 132.6, 117.2, 97.2, 66.0, 54.2, 52.1, 46.9; IR (Neat Film NaCl) 2952, 2359, 1738, 1611, 1434, 1224, 1144, 1060, 910 cm^{-1}; HRMS (MM: FAB +) *m/z* calc'd for $C_8H_{11}O_3NI$ $[M+H]^+$: 295.9784; found: 295.9775.



175i

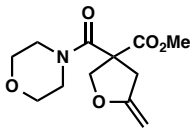
^1H NMR (500 MHz, C_6D_6) δ 4.44 (q, *J* = 2.0 Hz, 1H), 3.84 (d, *J* = 8.9 Hz, 1H), 3.79 – 3.75 (m, 2H), 3.02 (d, *J* = 0.7 Hz, 3H), 2.69 (dt, *J* = 15.9, 1.9 Hz, 1H), 2.42 (dt, *J* =

15.9, 1.6 Hz, 1H); ^{13}C NMR (126 MHz, C_6D_6) δ 166.1, 158.0, 117.3, 83.6, 75.1, 53.3, 46.9, 38.7; IR (Neat Film NaCl) 2959, 2249, 1747, 1682, 1435, 1231, 1046, 819 cm^{-1}; HRMS (MM: FAB +) *m/z* calc'd for $C_8H_{10}O_3N$ $[M+H]^+$: 168.0661; found: 168.0666.



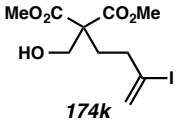
174j

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (q, *J* = 1.2 Hz, 1H), 5.97 (d, *J* = 1.6 Hz, 1H), 4.25 (d, *J* = 11.2 Hz, 1H), 3.88 (d, *J* = 11.2 Hz, 1H), 3.81 (s, 3H), 3.79 – 3.55 (m, 6H), 3.39 (s, br, 2H), 3.30 (dd, *J* = 15.5, 1.0 Hz, 1H), 3.06 (dd, *J* = 15.4, 1.1 Hz, 1H), 2.60 (s, br, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 167.7, 132.2, 99.9, 66.3, 66.1, 57.4, 53.1, 45.6, 37.2; IR (Neat Film NaCl) 2955, 2859, 1733, 1627, 1436, 1272, 1228, 1115, 1064, 999, 851 cm^{-1}; HRMS (MM: ESI-APCI +) *m/z* calc'd for $C_{12}H_{19}NO_5I$ $[M+H]^+$: 384.0302; found: 384.0315.



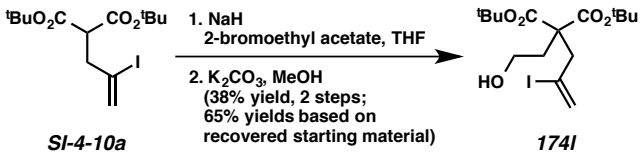
175j

^{1}H NMR (500 MHz, C_6D_6) δ 4.60 (d, *J* = 9.0 Hz, 1H), 4.55 (q, *J* = 1.8 Hz, 1H), 4.41 (d, *J* = 9.0 Hz, 1H), 3.94 (q, *J* = 1.7 Hz, 1H), 3.22 (s, br, 2H), 3.15 – 2.97 (m, 9H), 2.71 (s, br, 2H); ^{13}C NMR (101 MHz, C_6D_6) δ 171.6, 165.8, 160.7, 81.4, 75.2, 66.4, 66.0, 58.8, 52.5, 46.0, 43.5, 37.5; IR (Neat Film NaCl) 2857, 1733, 1651, 1435, 1274, 1115, 1018, 804 cm^{-1}; HRMS (MM: ESI-APCI +) *m/z* calc'd for $C_{12}H_{18}NO_5$ $[M+H]^+$: 256.1179; found: 256.1196.



174k

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.06 (q, *J* = 1.4 Hz, 1H), 5.72 (d, *J* = 1.7 Hz, 1H), 3.96 (s, 2H), 3.79 (d, *J* = 0.6 Hz, 6H), 2.49 – 2.43 (m, 2H), 2.20 – 2.13 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2, 126.4, 109.9, 64.9, 59.0, 52.9, 40.8, 31.5; IR (Neat Film NaCl) 2952, 1729, 1617, 1436, 1205, 1043, 898 cm^{-1}; HRMS (MM: FAB+) *m/z* calc'd for $C_{10}H_{16}IO_5$ $[M+H]^+$: 343.0043; found: 343.0031.

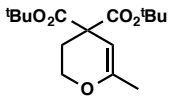


SI-4-10a ***174l***

To a solution of NaH (60% dispersion in mineral oil, 78.0 mg, 1.95 mmol, 2.00 equiv) in THF (3.26 mL) was added vinyl iodide **SI-4-10a** (374 mg, 0.977 mmol, 1.00 equiv), and the solution was stirred until gas evolution was complete. 2-Bromoethyl acetate (0.27 mL, 2.44 mmol, 2.50 equiv) was added to the reaction mixture at 0 °C and then, the solution was stirred at 23 °C for 24 h. The reaction was quenched with sat. NH_4Cl at 0 °C and the mixture was extracted with EtOAc (3 x 3.00 mL), the combined organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (1:20 EtOAc:hexanes) to give dialkylated malonate and recovered **SI-4-10a**.

To a solution of dialkylated malonate intermediate (344 mg, 0.735 mmol, 1.00 equiv) in MeOH (2.50 mL) was added K_2CO_3 (203 mg, 1.47 mmol, 2.00 equiv) and the solution was stirred at 23 °C for 24 h. The reaction mixture was diluted with CH_2Cl_2 (3.00 mL) and the mixture was extracted with CH_2Cl_2 (3 x 2.00 mL), the combined organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated *in*

vacuo. The residue was purified by silica gel flash chromatography (1:20 → 1:8 → 1:4 EtOAc:hexanes) to give malonate **174l** (159 mg, 38% yield, 2 steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.14 (q, *J* = 1.4 Hz, 1H), 5.91 (d, *J* = 1.7 Hz, 1H), 3.72 (t, *J* = 6.7 Hz, 2H), 3.17 (d, *J* = 1.2 Hz, 2H), 2.28 (t, *J* = 6.7 Hz, 2H), 1.65 (s, br, 1H), 1.47 (s, 18H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0, 130.5, 102.2, 82.5, 59.2, 57.7, 46.9, 34.7, 28.1; IR (Neat Film NaCl) 3447, 2977, 1726, 1368, 1250, 1145, 843 cm^{-1}; HRMS (MM: FAB +) *m/z* calc'd for $C_{16}H_{28}IO_5$ $[M+H]^+$: 427.0982; found: 427.0985.



175l

^{1}H NMR (500 MHz, CD_2Cl_2) δ 4.68 (h, *J* = 0.9 Hz, 1H), 4.02 – 3.96 (m, 2H), 2.10 – 2.04 (m, 2H), 1.76 (d, *J* = 1.0 Hz, 3H), 1.43 (s, 18H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 170.6, 153.8, 94.6, 81.7, 64.1, 52.5, 28.7, 28.1, 20.6; IR (Neat Film NaCl) 2977, 2933, 1728, 1369, 1266, 1146, 1108, 1088, 847 cm^{-1}; HRMS (MM: FAB +) *m/z* calc'd for $C_{16}H_{27}O_5$ $[M+H]^+$: 299.1858; found: 299.1835.

4.5. References and Notes

(1) Selected recent reviews: (a) Han, F.-S. *Chem. Soc. Rev.* **2013**, *42*, 5270–5298. (b) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417–1492. (c) Hartwig, J. F. *Nature* **2008**, *455*, 314–322. (d) Terao, J.; Kambe, N. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 663–672.

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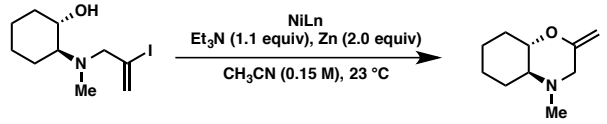
(14) Importantly, if the $Ni(COD)_2$ catalyst was omitted, no carbon–oxygen bond formation was observed. Addition of other additives such as Mg and CuI decreased the yields (36% and 0% yield, respectively).

(15) Intramolecular etherification of vinyl iodide **170b** proceeded with 5 mol % of NiI_2 or $NiBr_2$(dme) to furnish vinyl ether **171b** (entries 1 and 2). An increased rate of cycloetherification was observed with 10 mol % of $NiBr_2$(dme) (entries 2 and 3). Unfortunately, attempts to convert vinyl iodide **170b** to enol ether **171b** outside a N_2-filled glove box were unsuccessful (entries 4 and 5).



170b *171b*

entry	NiLn	Ni mol %	time	yield (%)[a]
1[b]	NiI_2	5	16 h	60
2[b]	$NiBr_2$(dme)	5	48 h	53
3[b]	$NiBr_2$(dme)	10	16 h	51
4[c]	NiI_2	5	24 h	0
5[c]	$NiBr_2$(dme)	5	24 h	0

[a] Yield of isolated product. [b] Reactions were performed in a N_2-filled glove box. [c] Reactions were performed under argon outside a N_2-filled glove box.

(16) No significant improvement in yield or catalyst turnover was observed when various ligands (e.g., various NHC, PYBOX, BOX, diamine, BiOX ligands) were employed.

(17) Since intramolecular etherifications of aminocyclohexanols **170a** or **170b** proceeded even without Zn powder despite low yields and catalyst turnover (Table 1), we envision that Zn powder likely plays an important role as a scavenger of the forming HI.

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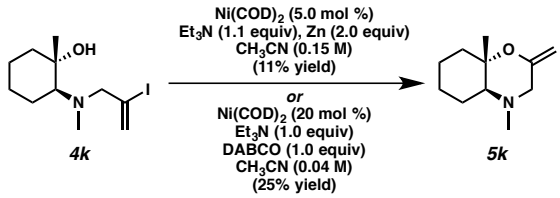
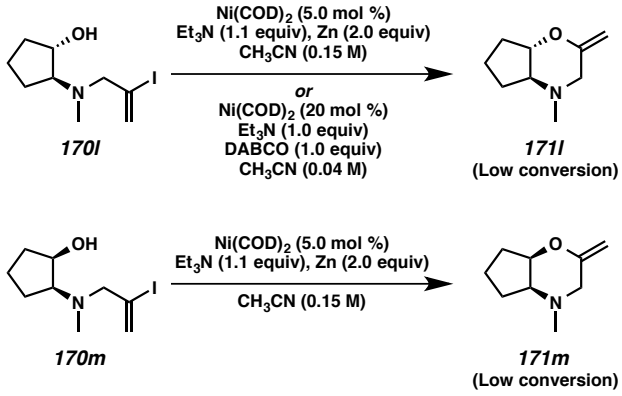
(20) An intramolecular cross-coupling of **170k** afforded the desired product **171k** in low yield under our standard reaction conditions.



(21) Surprisingly, the cycloetherification of *trans*- and *cis*-aminocyclopentanol derived substrates resulted in very low conversion.



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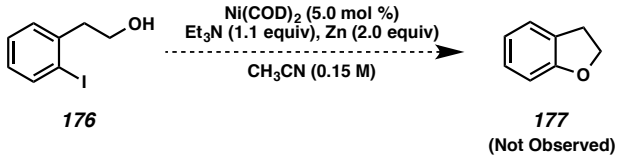
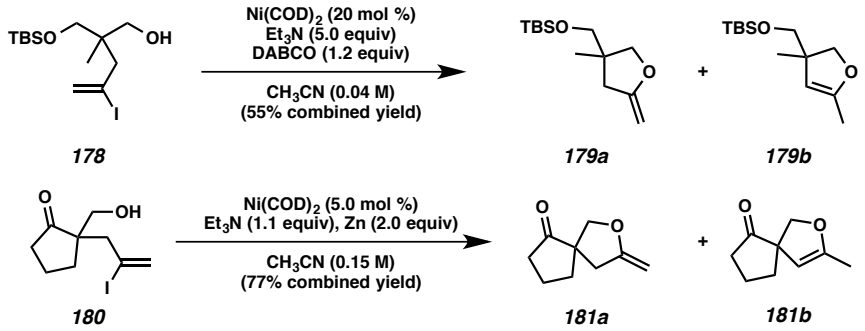
(24) Although we attempted to construct 2,3-dihydrobenzofuran **177** from aryl iodide **176** under our standard reaction conditions, only unreacted starting material was recovered.



176 ***177*** (Not Observed)

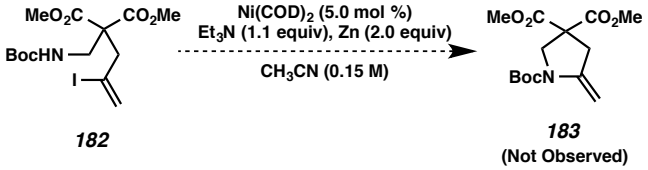
(25) Substrates containing alkyl- or mono-ketone substituents instead of a malonate provided a mixture of isomers upon subjection to carbon–oxygen cross-coupling conditions.



178 ***179a*** ***179b***

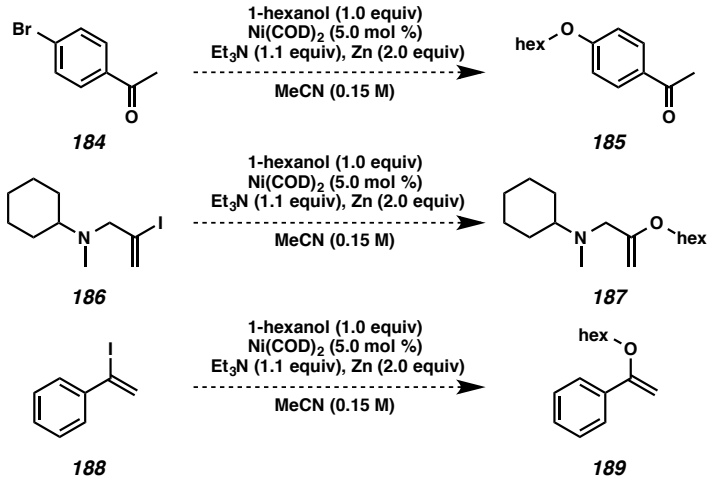
180 ***181a*** ***181b***

(26) Unfortunately, the cyclization reaction of a malonate substrate bearing a nitrogen nucleophile (**182**) was unsuccessful.



182 ***183*** (Not Observed)

(27) An intermolecular etherification of MacMillan's substrate **184** (ref. 8) with 1-hexanol under our reaction conditions was not successful. Additionally, attempted intermolecular cross-coupling processes of **186** and **188** with 1-hexanol under our standard reaction conditions resulted in no reaction.

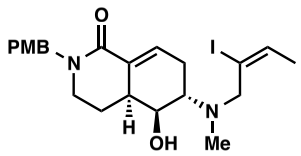

Br
O
1-hexanol (1.0 equiv)
Ni(COD)2 (5.0 mol %)
Et3N (1.1 equiv), Zn (2.0 equiv)
MeCN (0.15 M)
hex
O
O
184
185
1-hexanol (1.0 equiv)
Ni(COD)2 (5.0 mol %)
Et3N (1.1 equiv), Zn (2.0 equiv)
MeCN (0.15 M)
N
I
N
O
hex
186
187
1-hexanol (1.0 equiv)
Ni(COD)2 (5.0 mol %)
Et3N (1.1 equiv), Zn (2.0 equiv)
MeCN (0.15 M)
I
hex
O
188
189

APPENDIX 8

Spectra Relevant to Chapter 4:

Ni-Catalyzed Intramolecular C–O Bond Formation:

Synthesis of Cyclic Enol Ethers



167

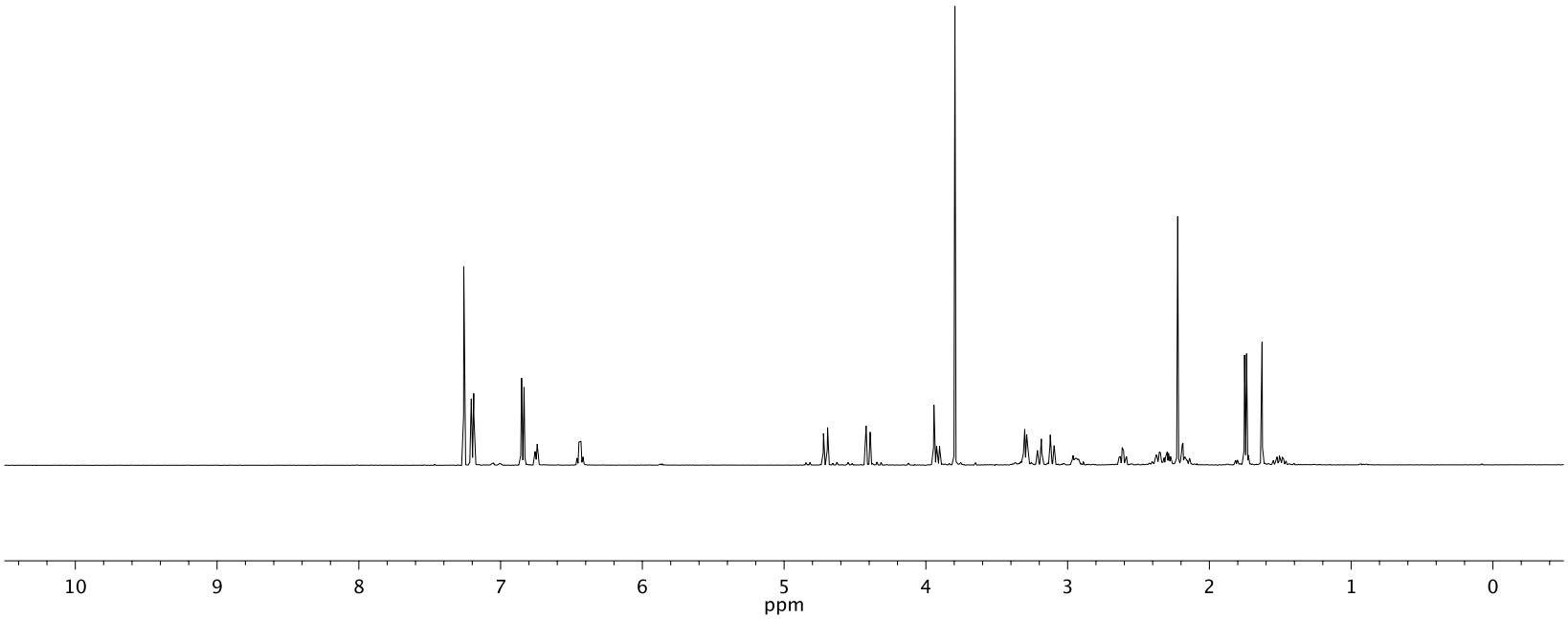


Figure A8.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **167**.

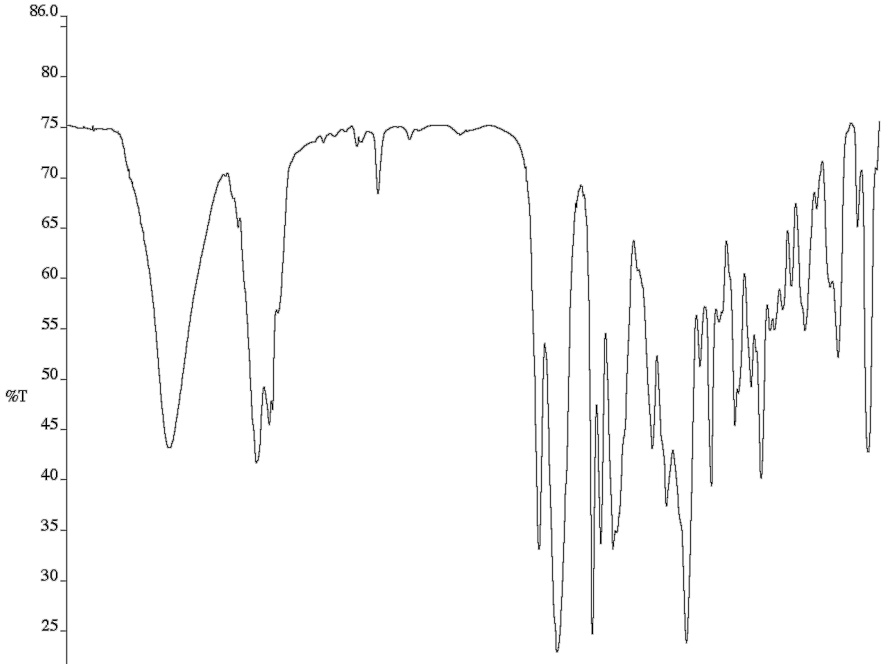


Figure A8.2. Infrared spectrum (Thin Film, NaCl) of compound **167**.

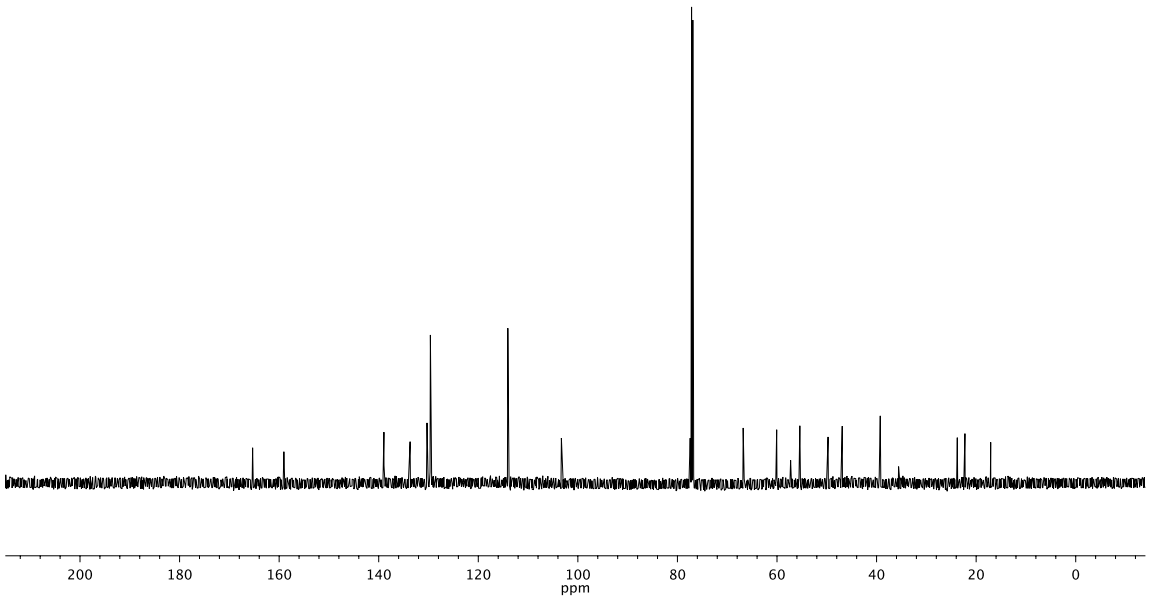


Figure A8.3. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **167**.

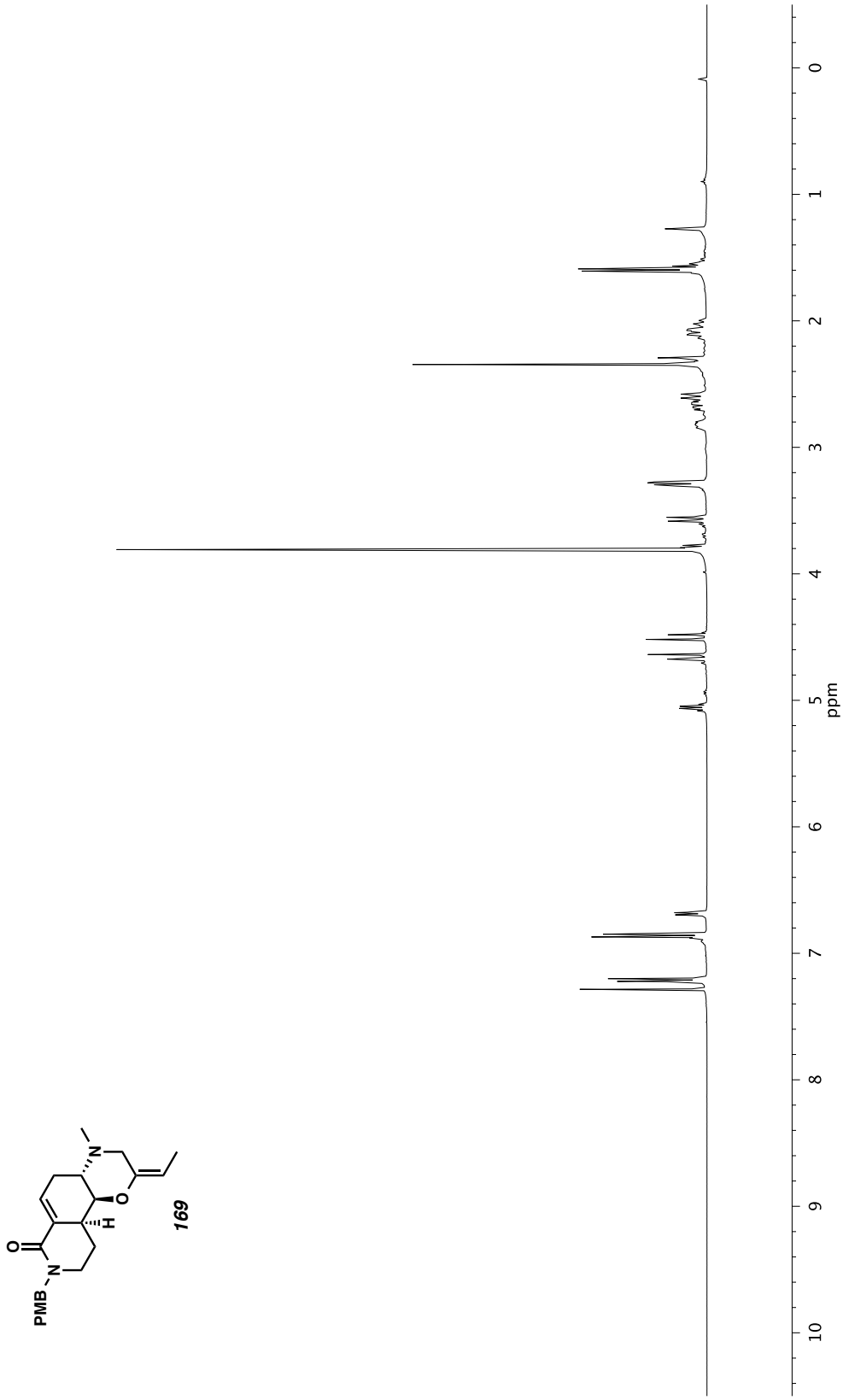


Figure A8.4. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **169**.

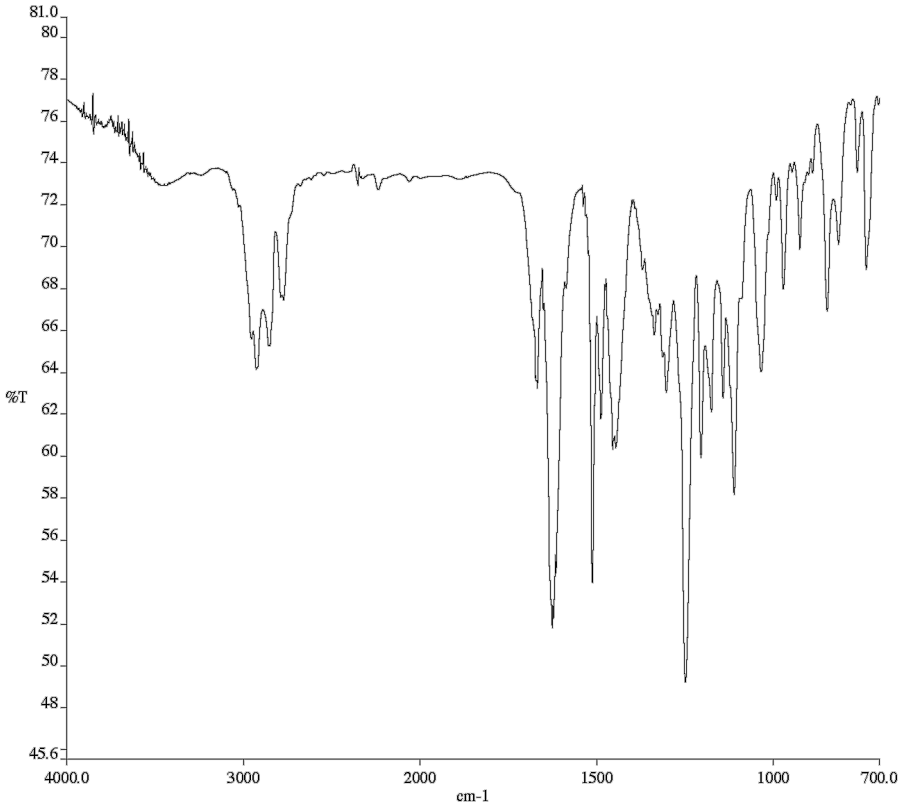


Figure A8.5. Infrared spectrum (Thin Film, NaCl) of compound **169**.

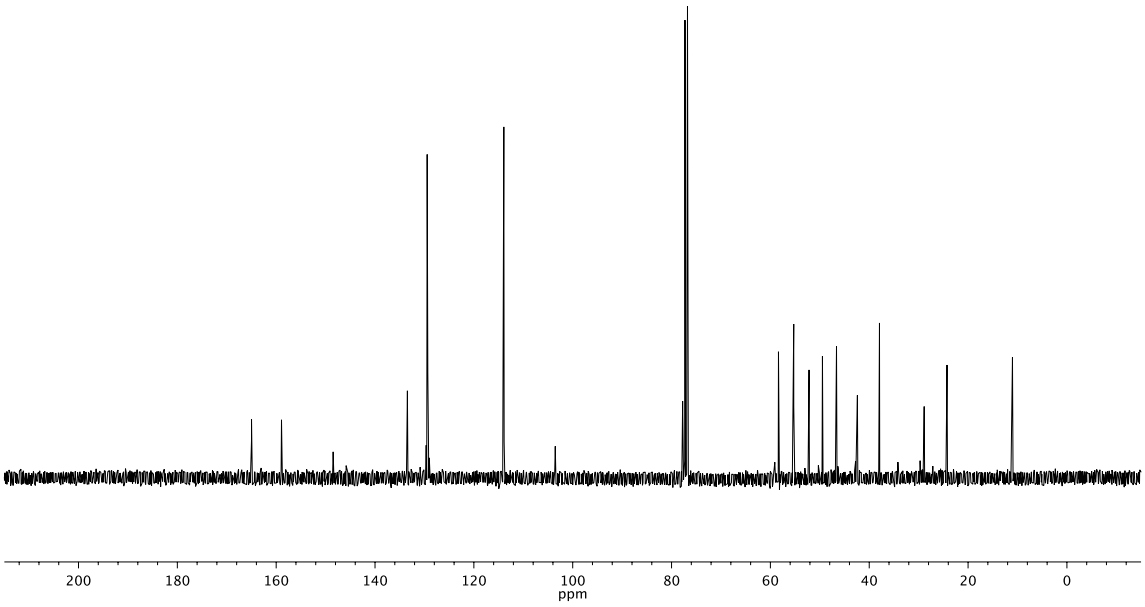


Figure A8.6. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **169**.

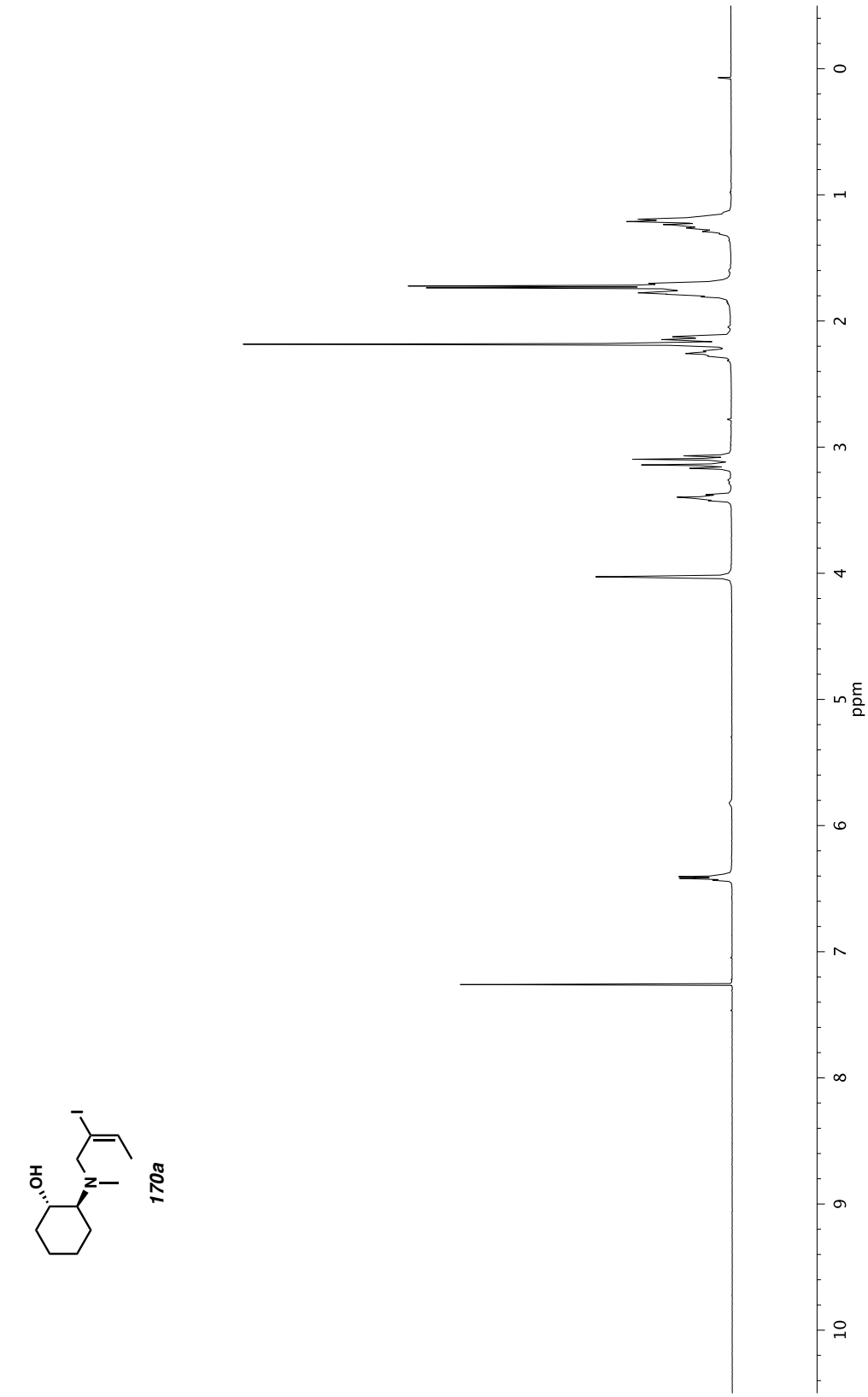


Figure A8.7. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **170a**.

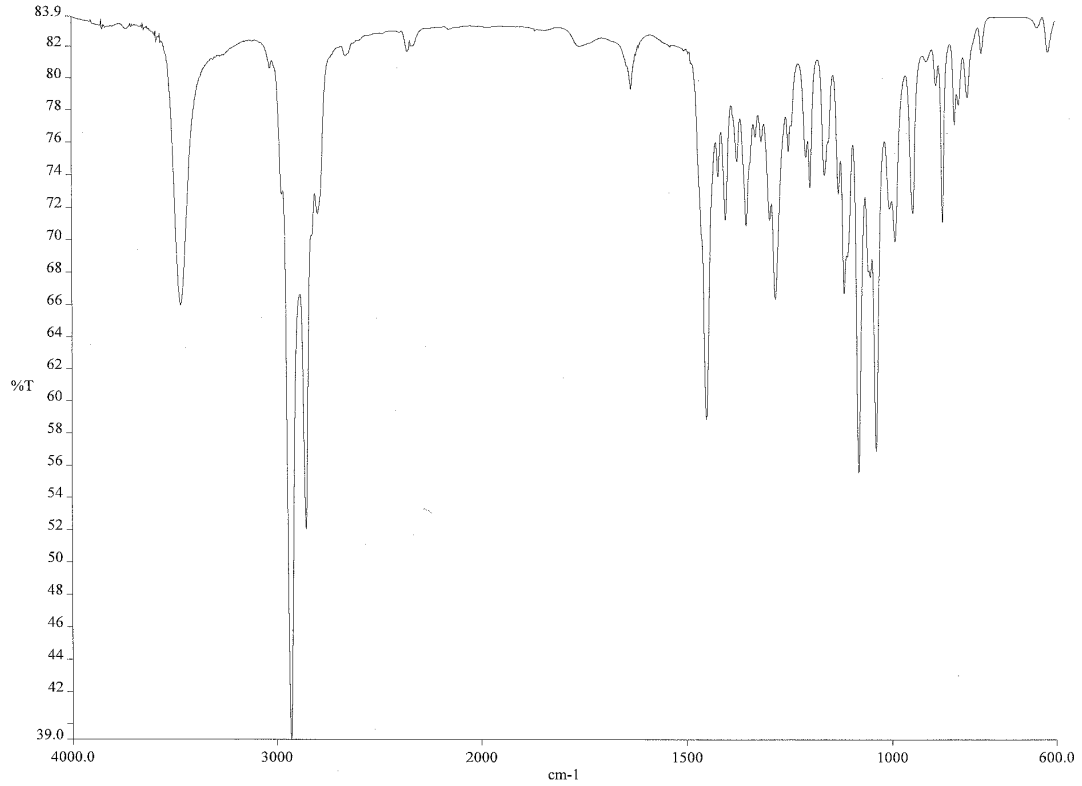


Figure A8.8. Infrared spectrum (Thin Film, NaCl) of compound **170a**.

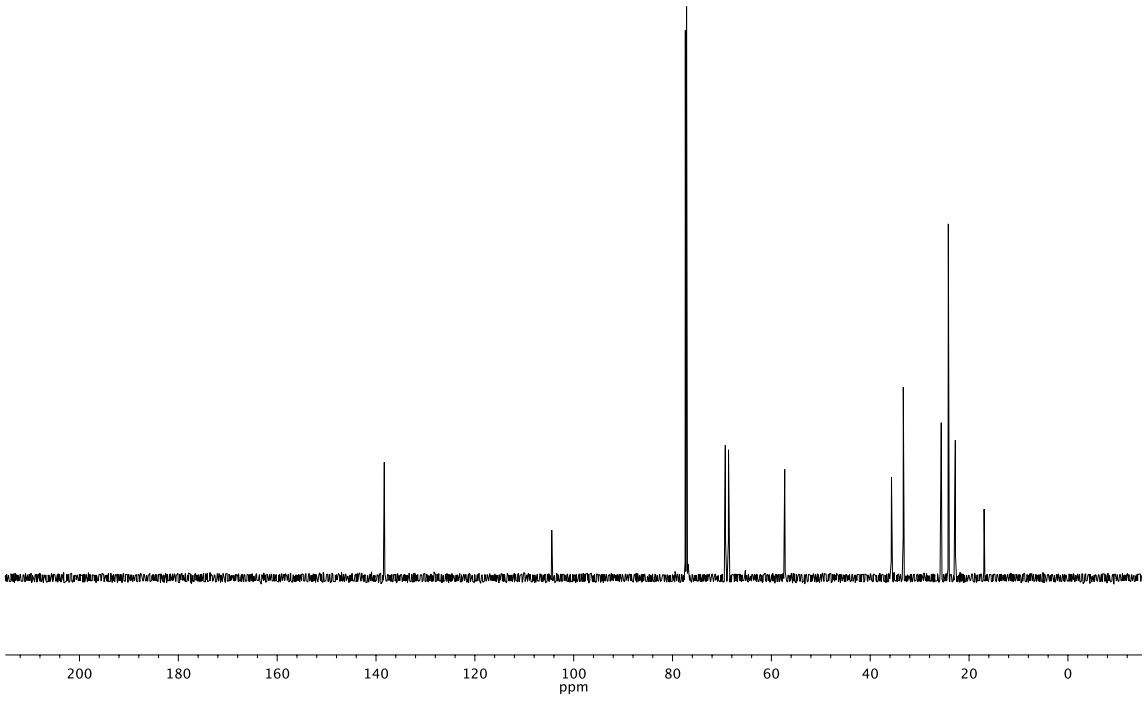


Figure A8.9. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **170a**.

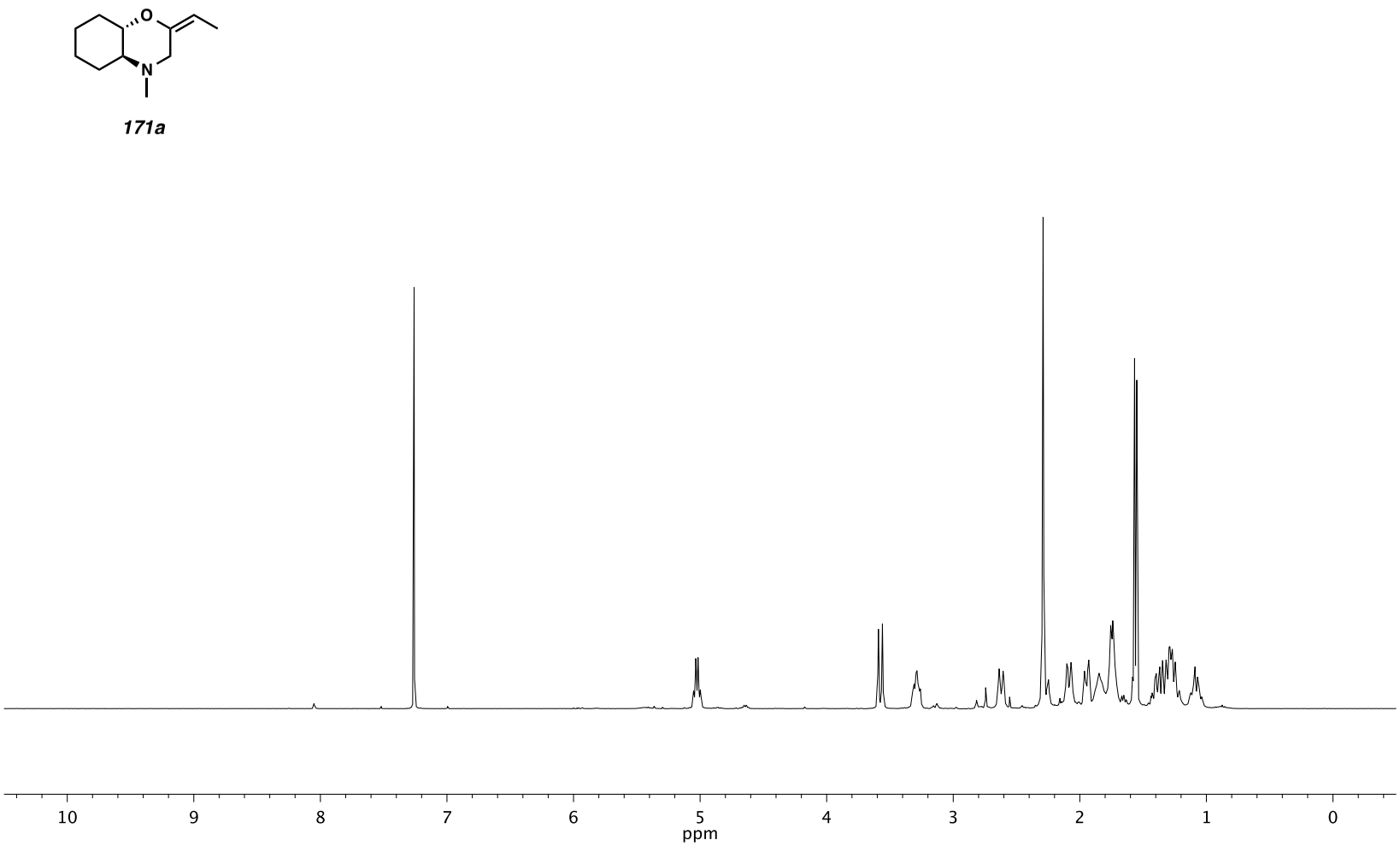


Figure A8.10. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **171a**.

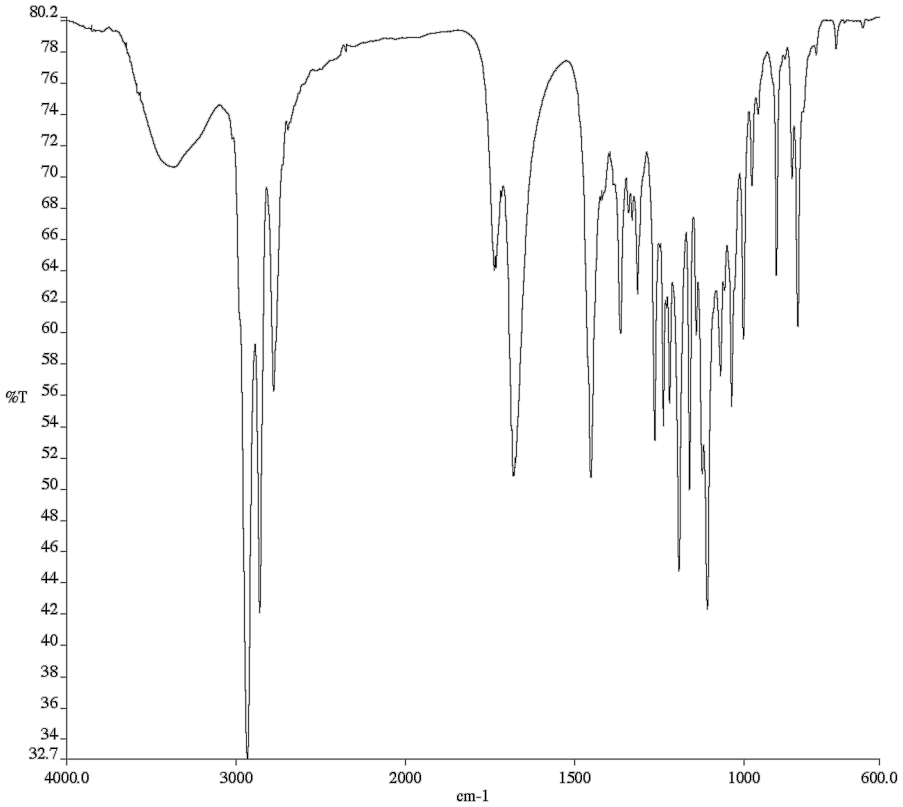


Figure A8.11. Infrared spectrum (Thin Film, NaCl) of compound **171a**.

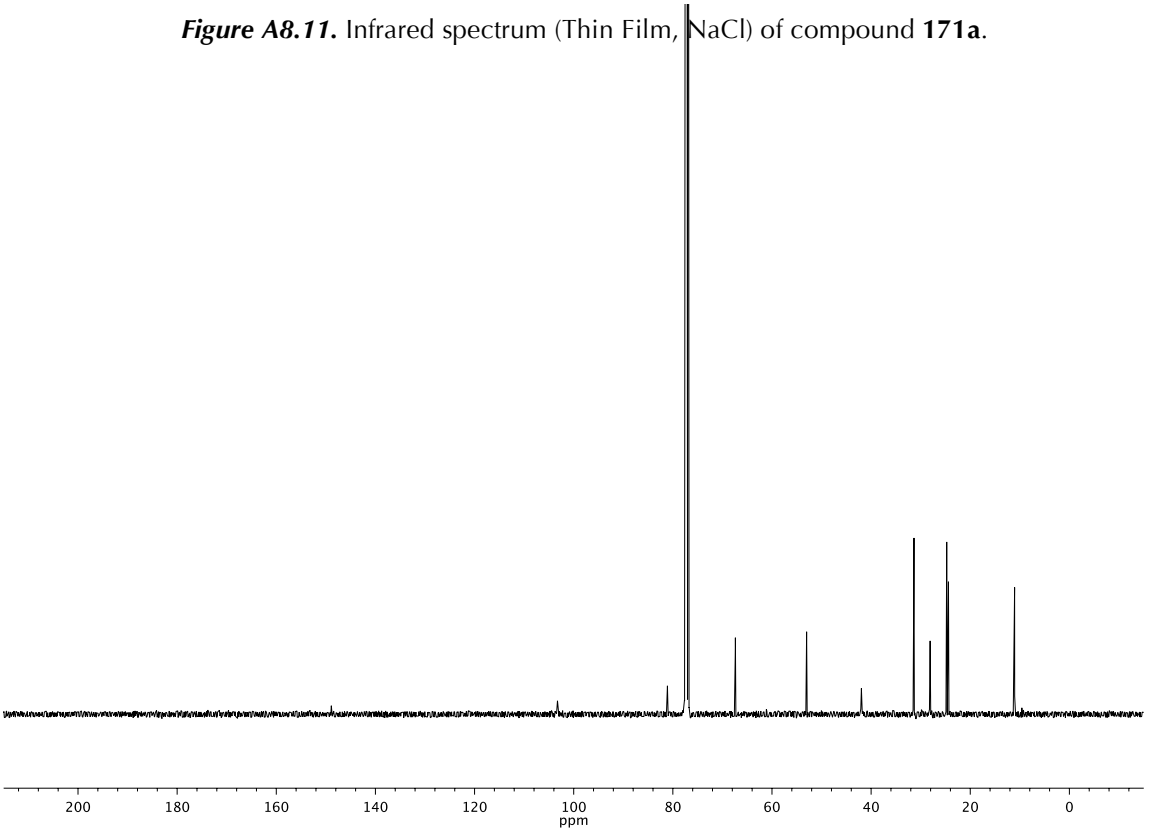


Figure A8.12. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **171a**.

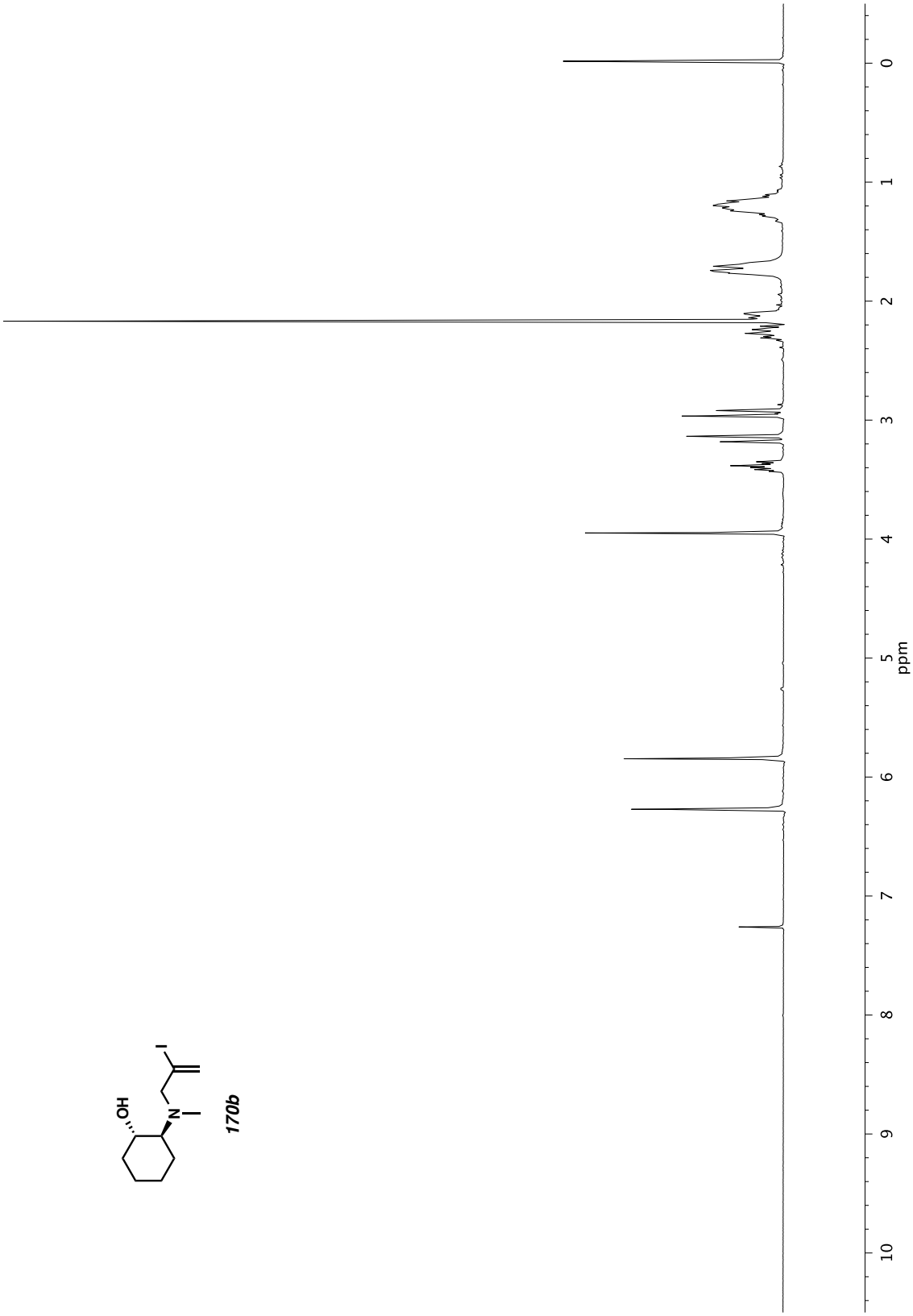


Figure A8.13. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **170b**.

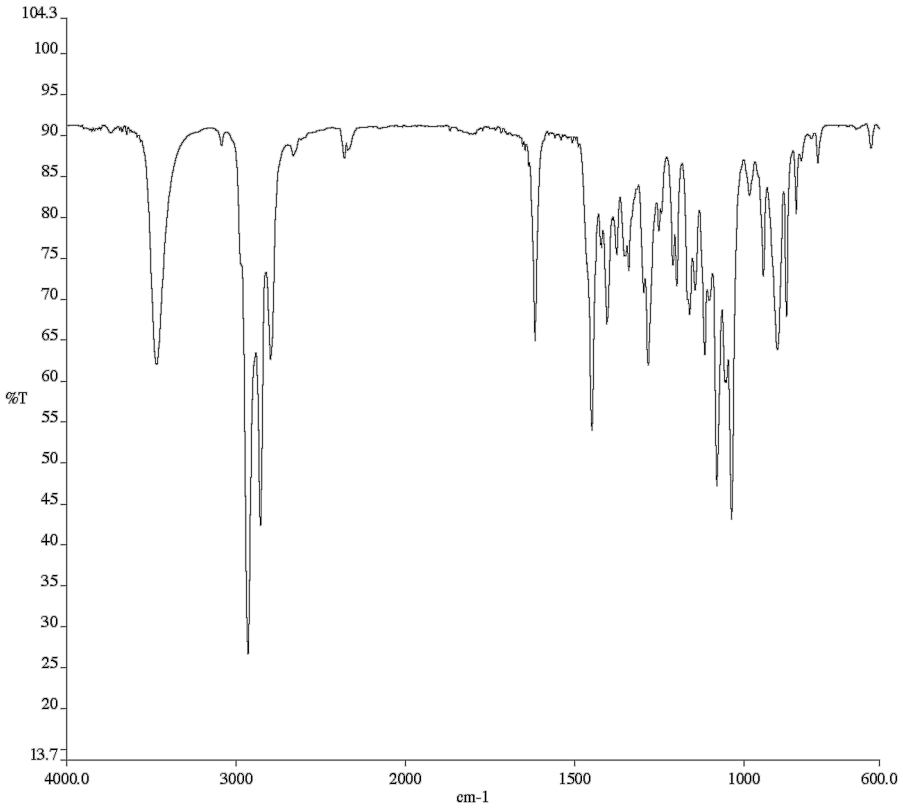


Figure A8.14. Infrared spectrum (Thin Film, NaCl) of compound **170b**.

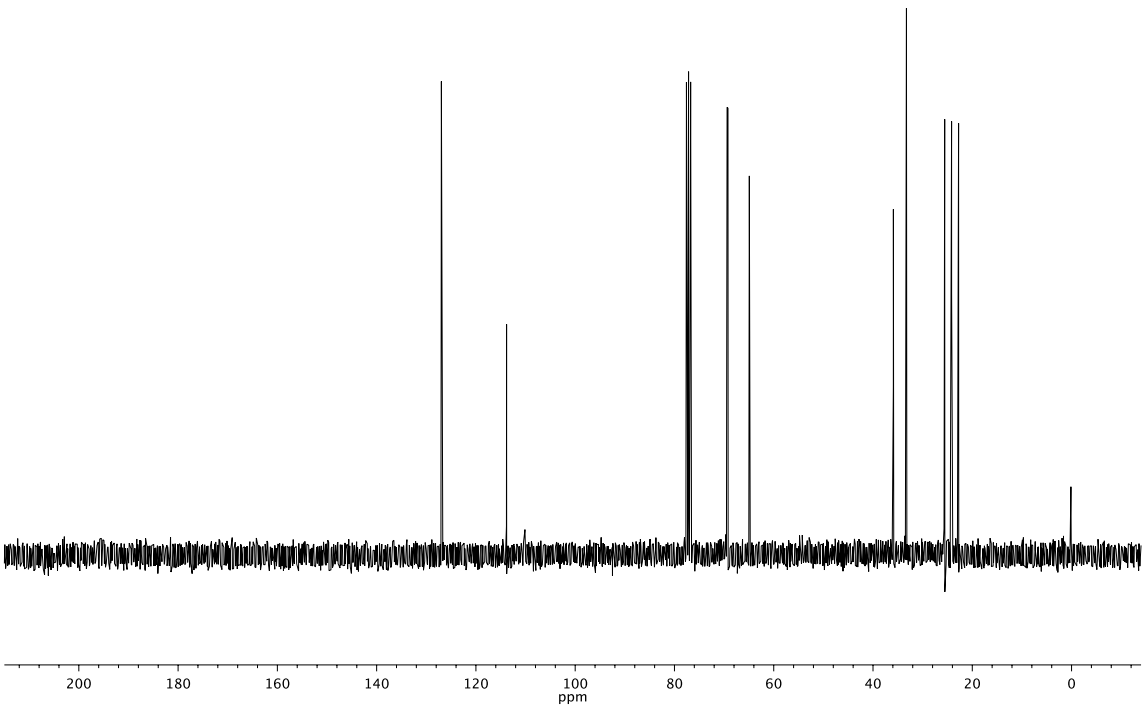
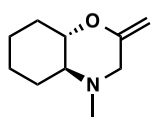


Figure A8.15. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **170b**.



171b

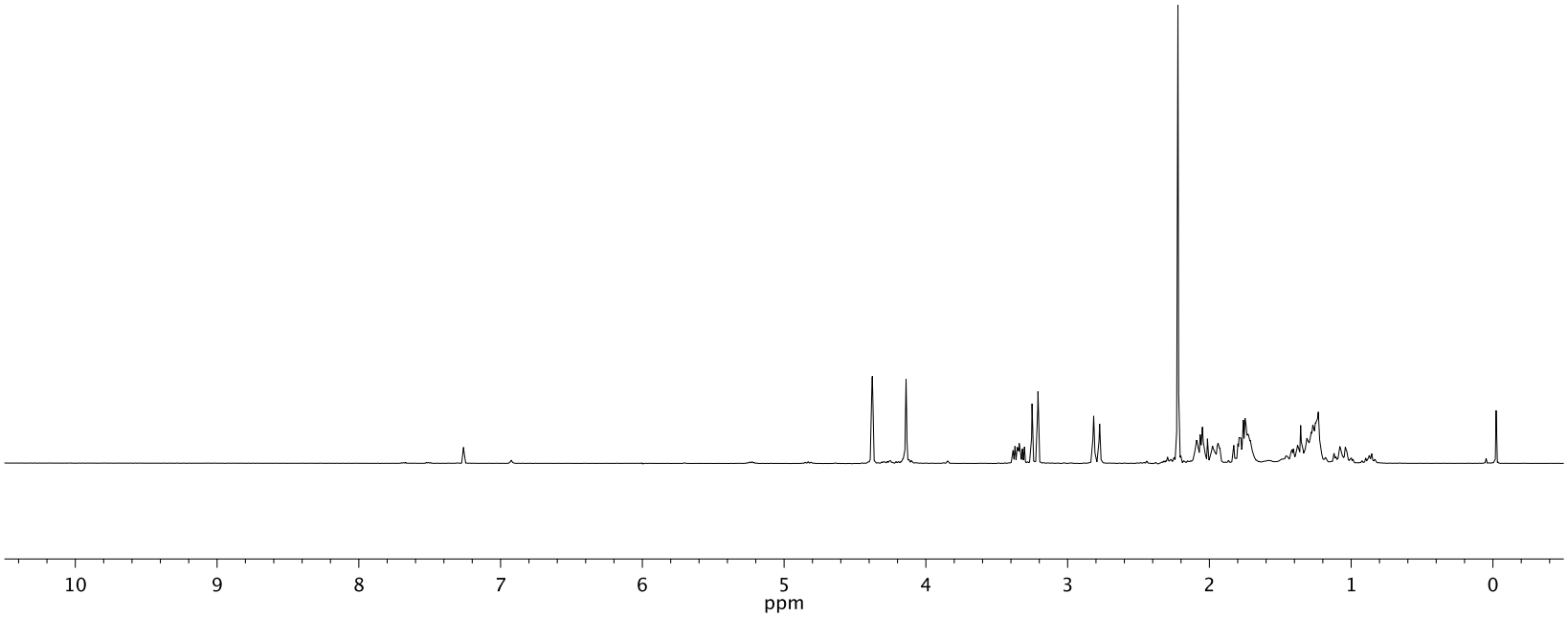


Figure A8.16. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **171b**.

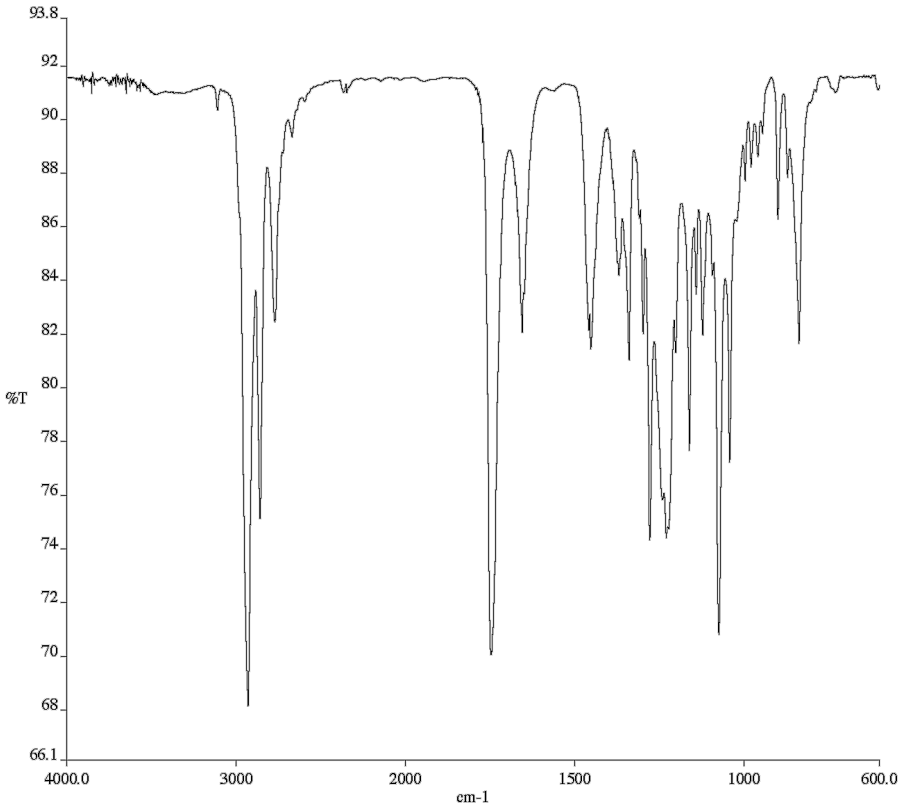


Figure A8.17. Infrared spectrum (Thin Film, NaCl) of compound **171b**.

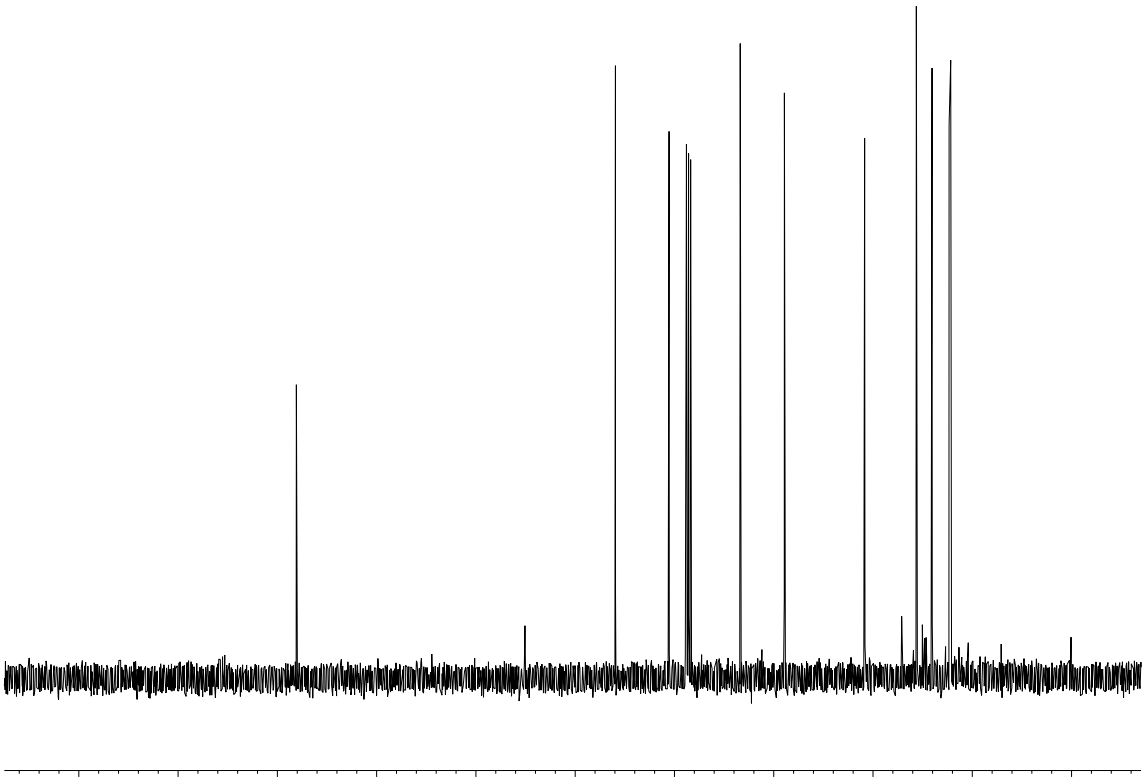


Figure A8.18. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **171b**.

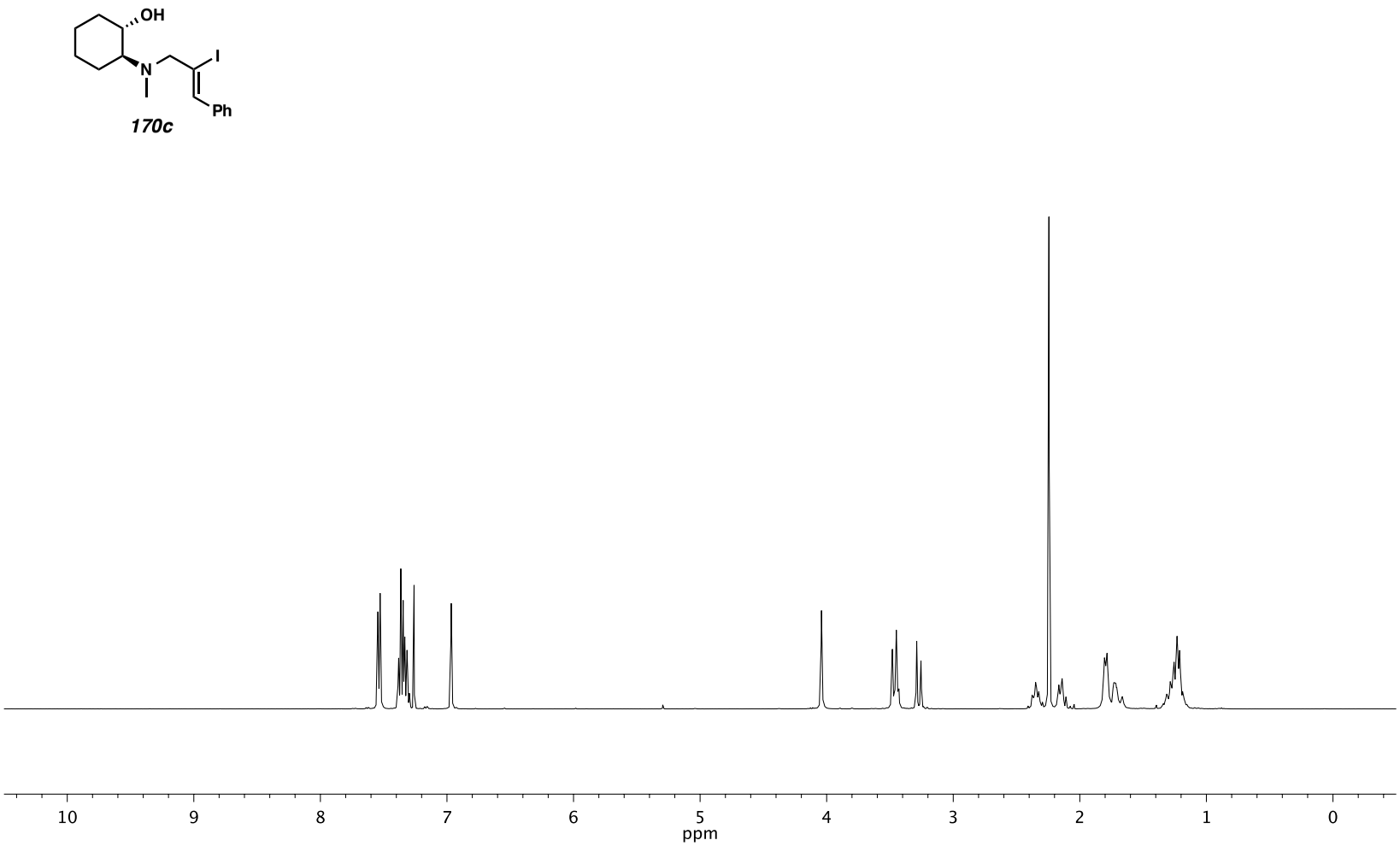


Figure A8.19. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **170c**.

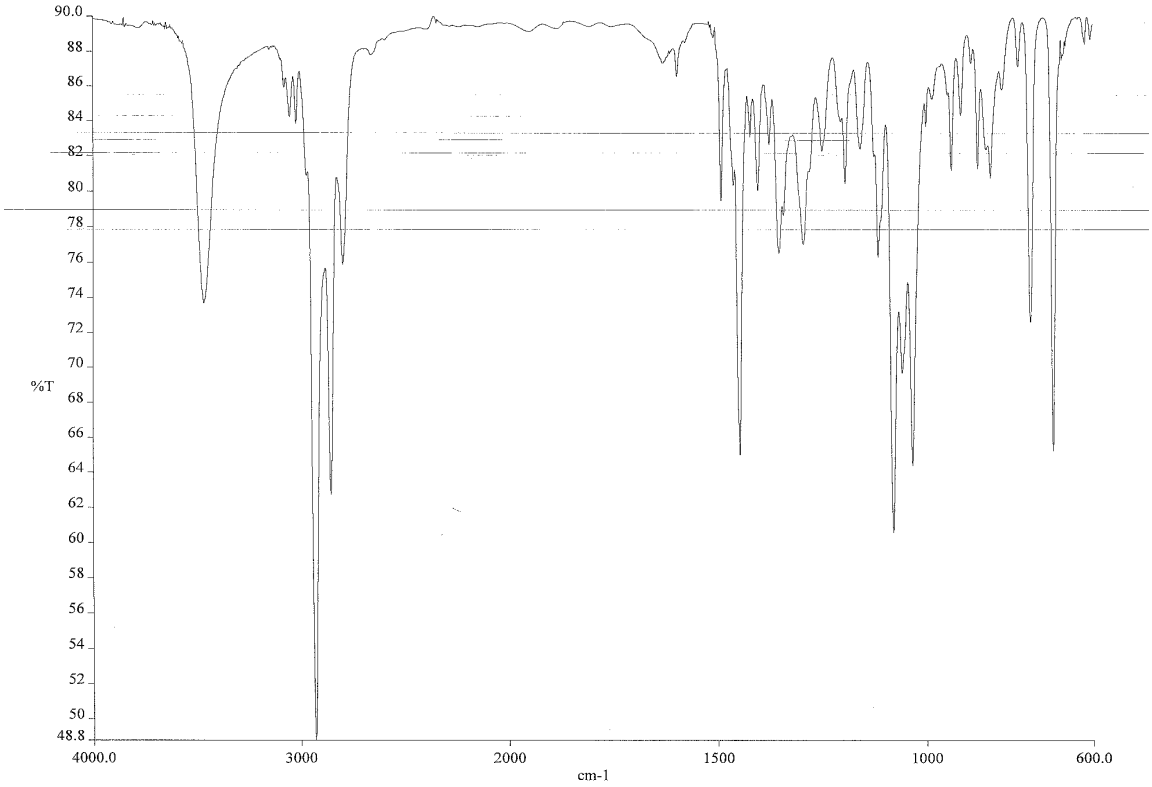


Figure A8.20. Infrared spectrum (Thin Film, NaCl) of compound **170c**.

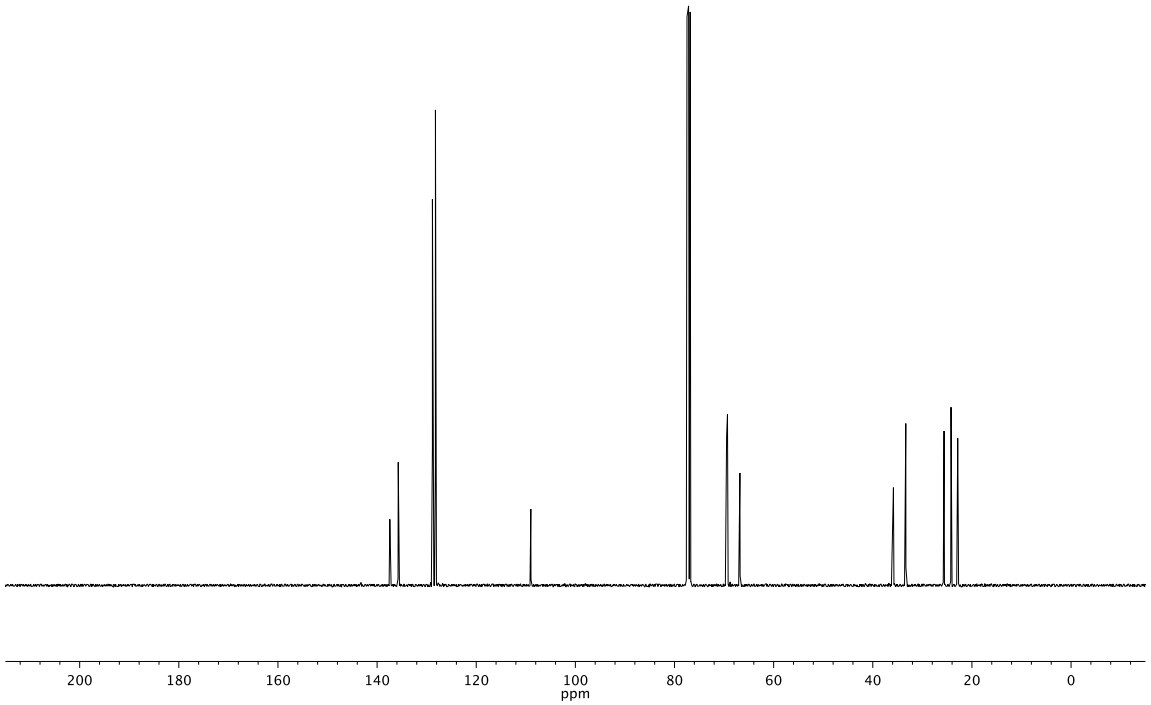


Figure A8.21. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **170c**.

Figure A8.22. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **171c**.

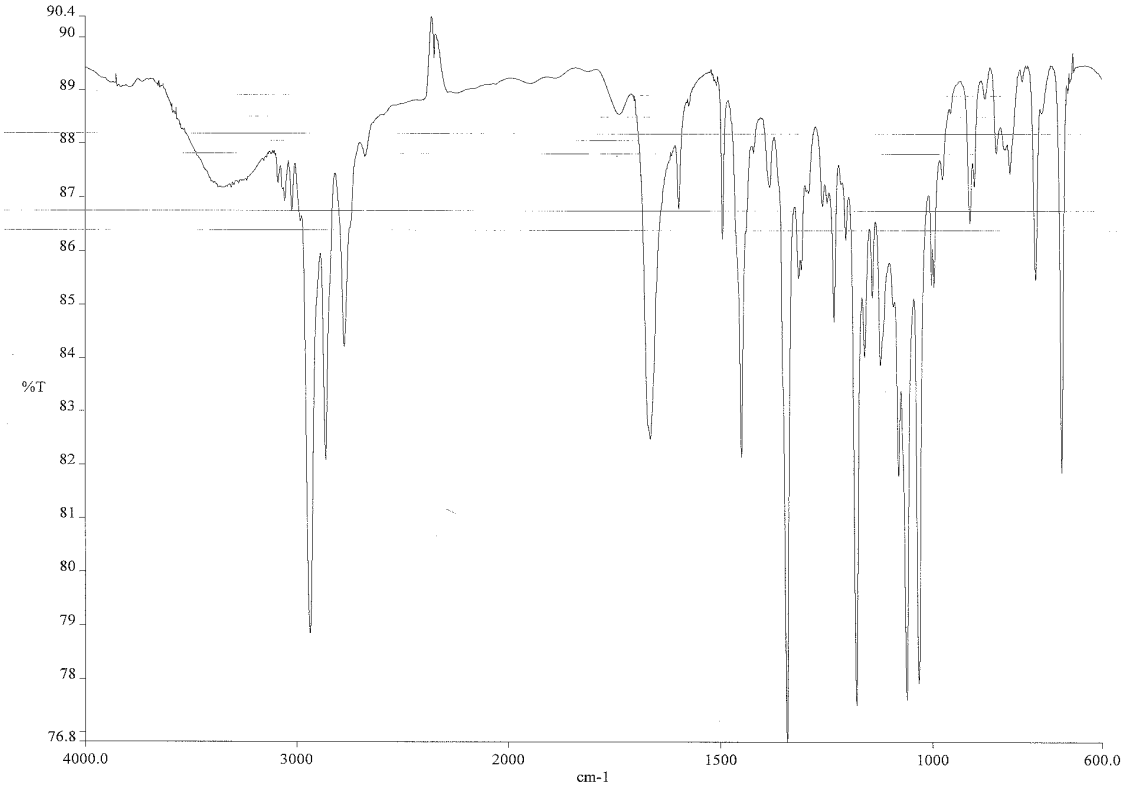


Figure A8.23. Infrared spectrum (Thin Film, NaCl) of compound **171c**.

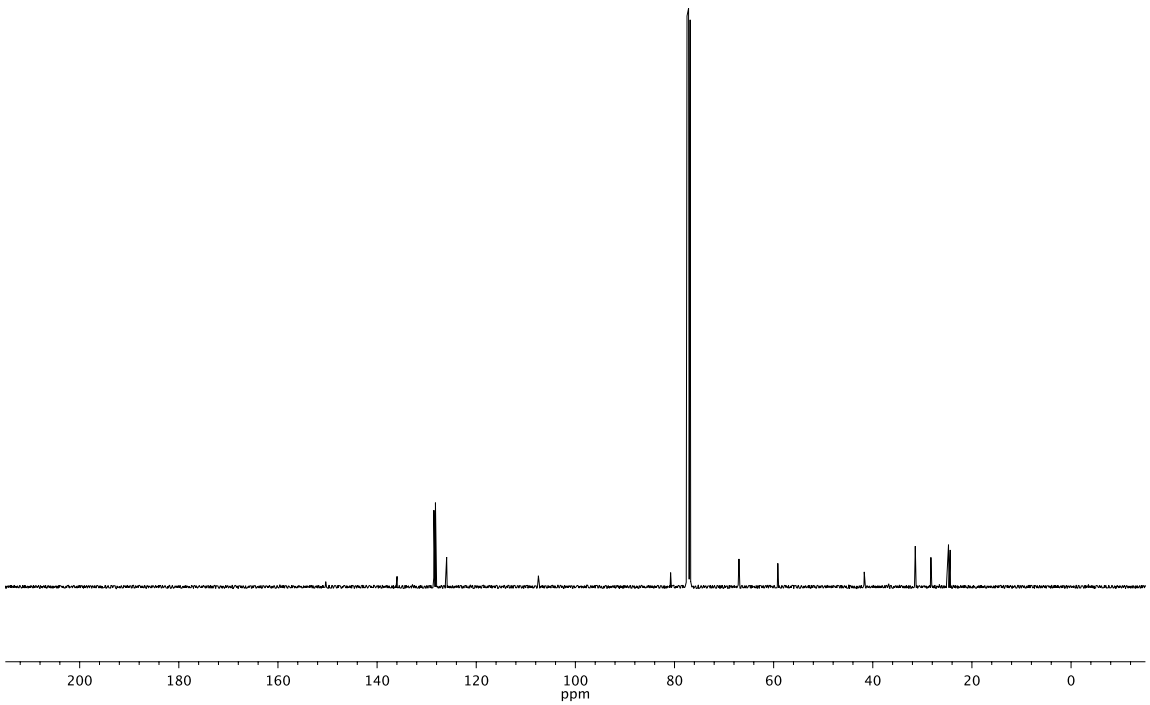


Figure A8.24. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **171c**.

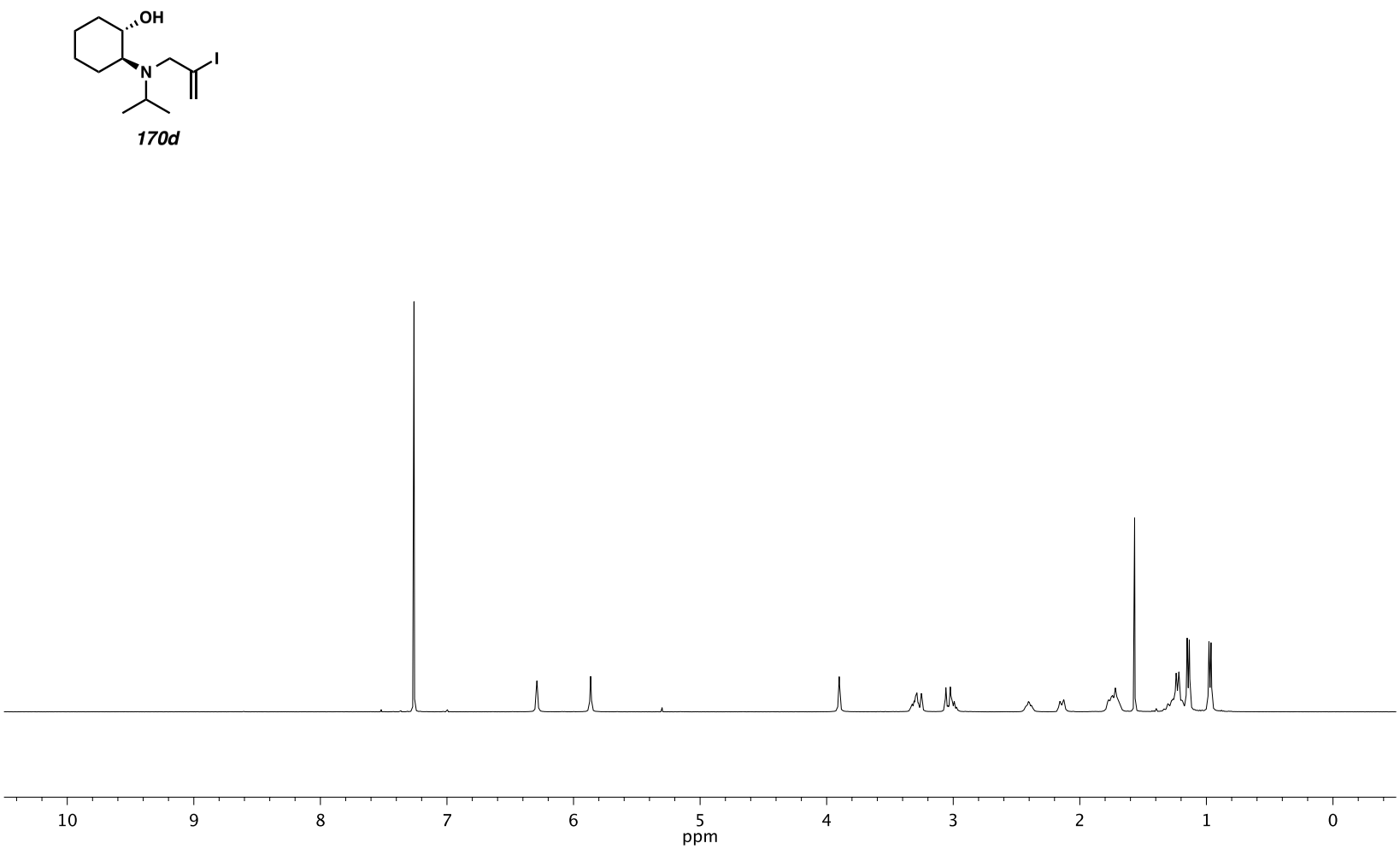


Figure A8.25. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **170d**.

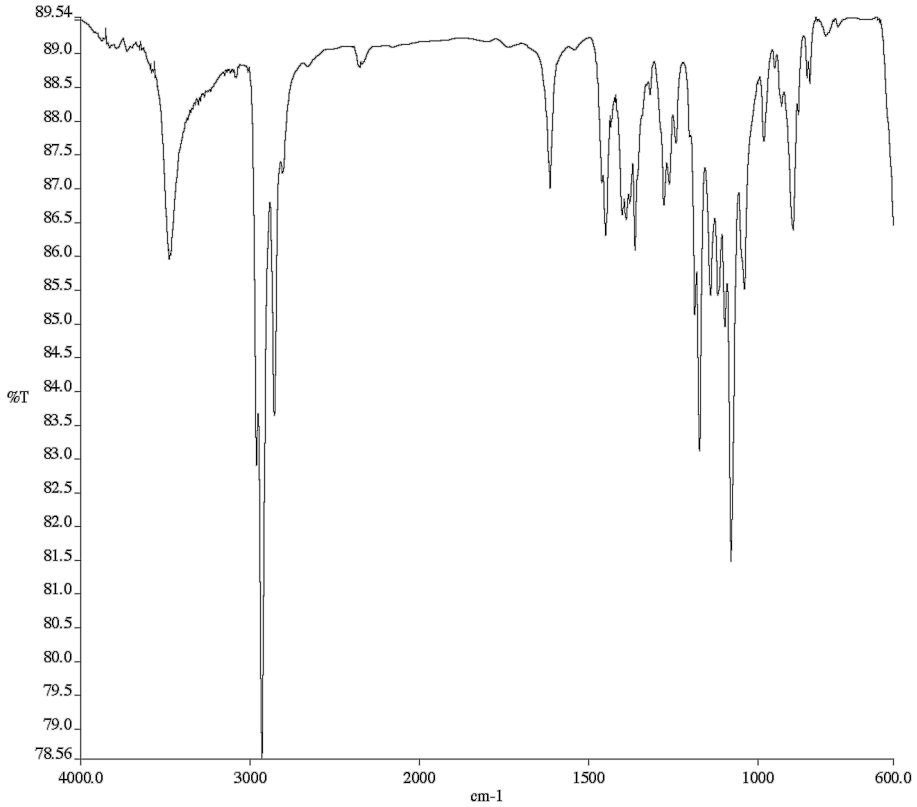


Figure A8.26. Infrared spectrum (Thin Film, NaCl) of compound **170d**.

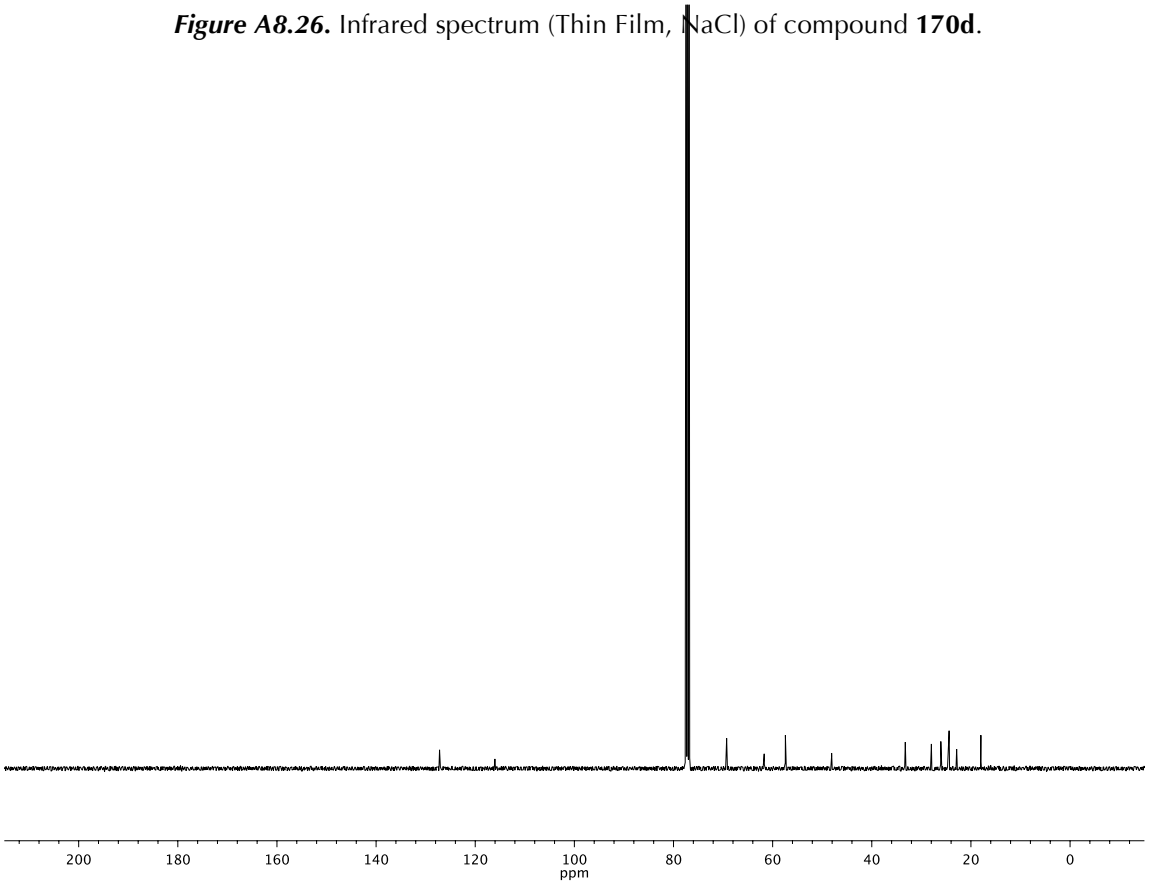


Figure A8.27. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **170d**.

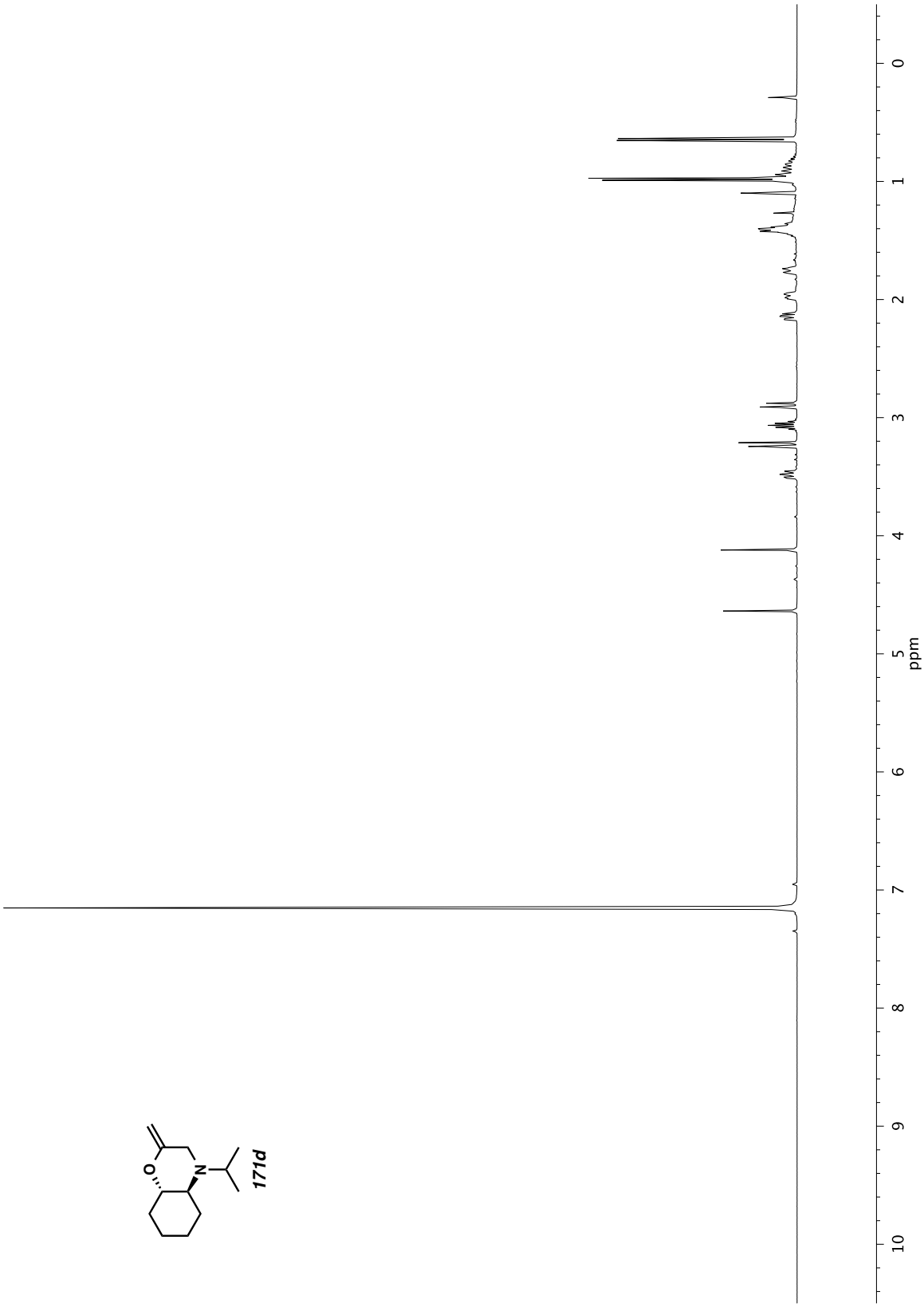


Figure A8.28. ^{1}H NMR (400 MHz, C_6D_6) of compound **171d**.

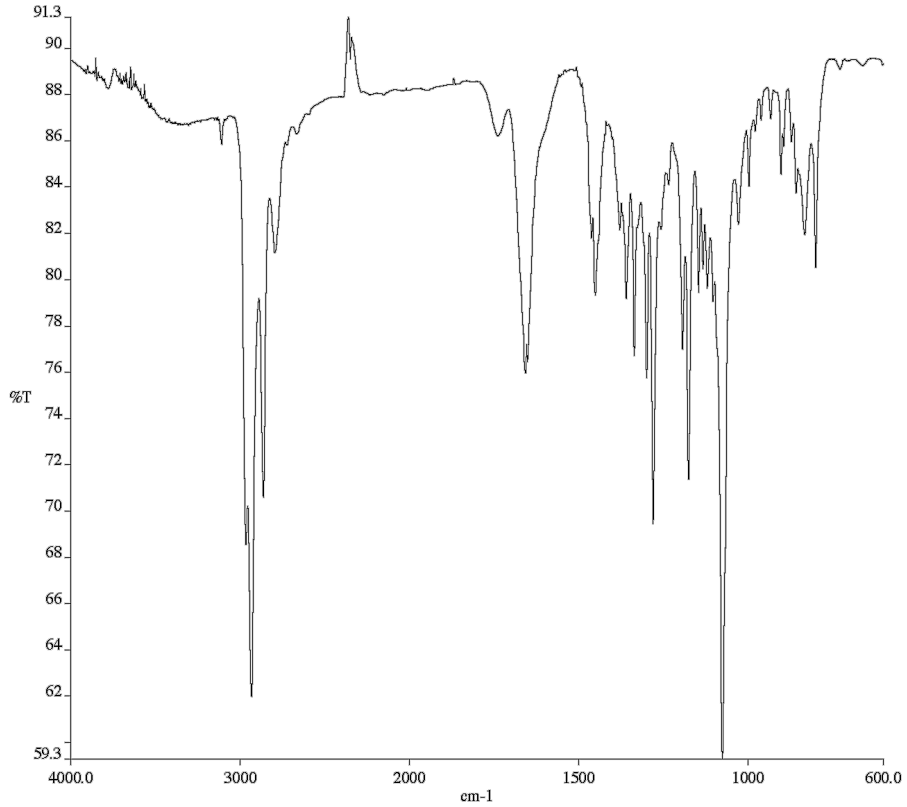


Figure A8.29. Infrared spectrum (Thin Film, NaCl) of compound **171d**.

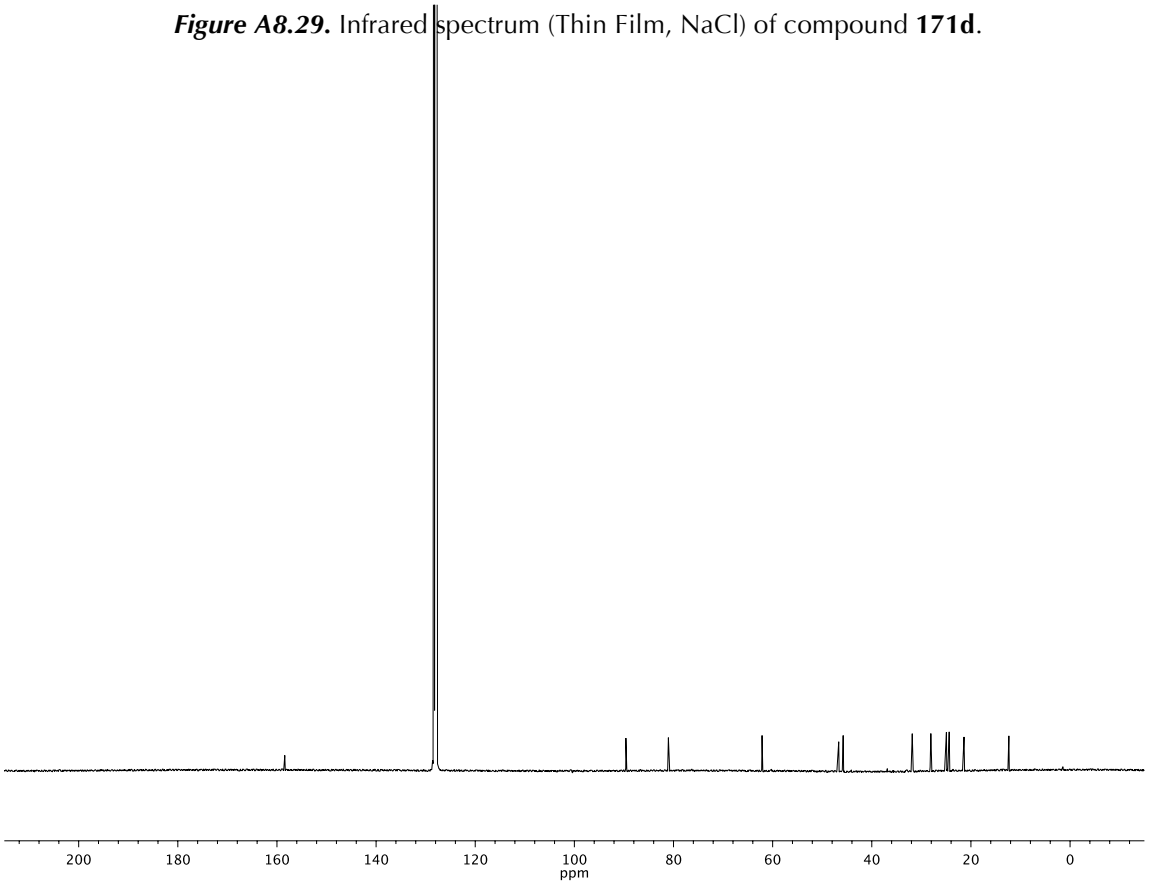


Figure A8.30. ^{13}C NMR (101 MHz, C_6D_6) of compound **171d**.

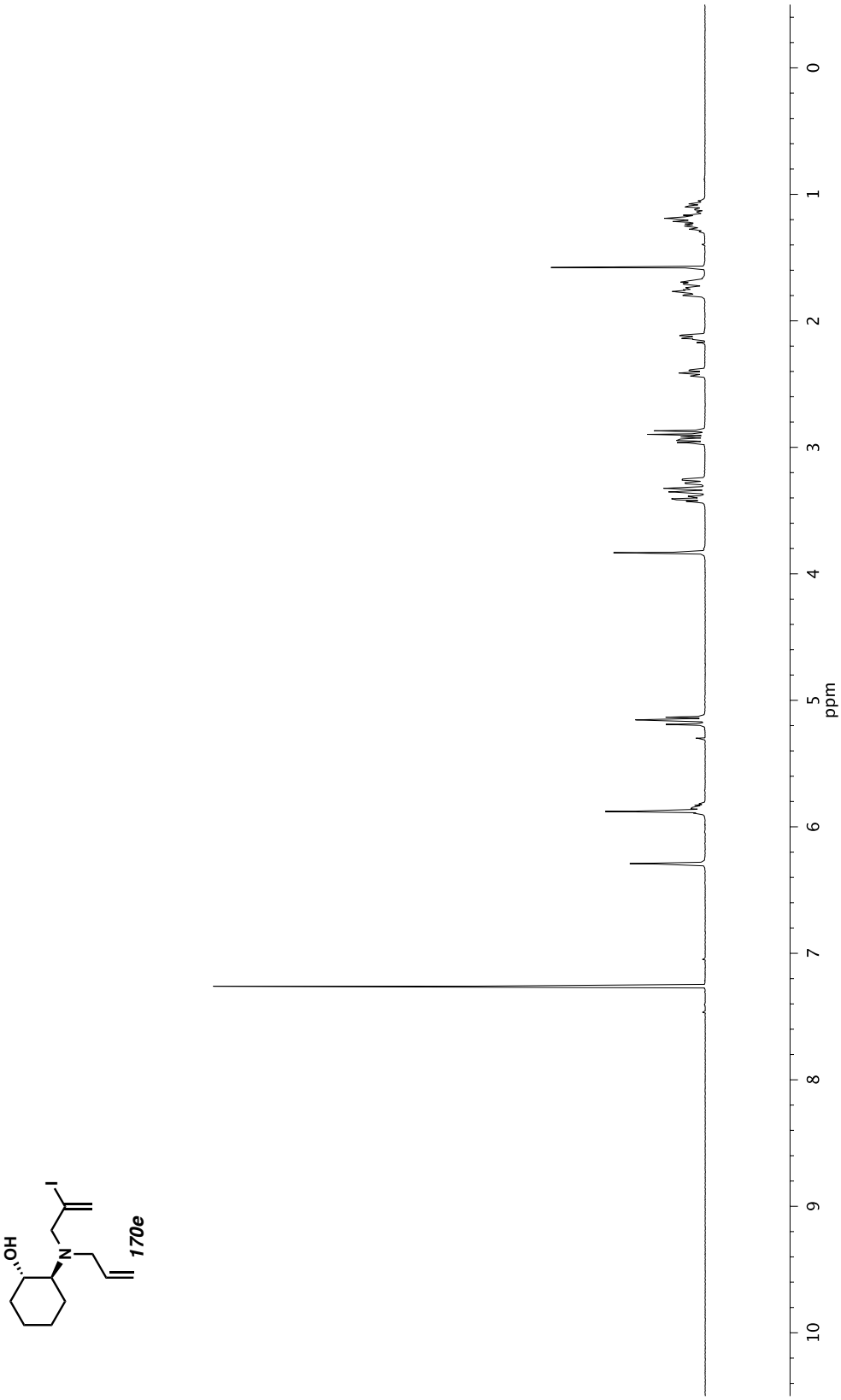


Figure A8.31. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **170e**.

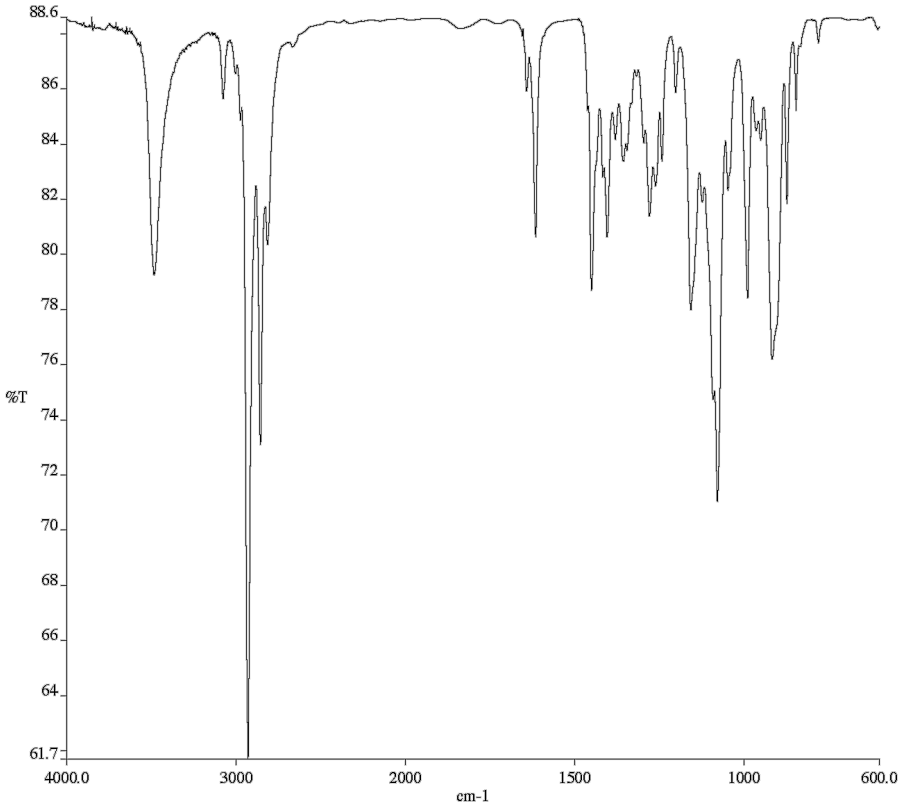


Figure A8.32. Infrared spectrum (Thin Film, NaCl) of compound **170e**.

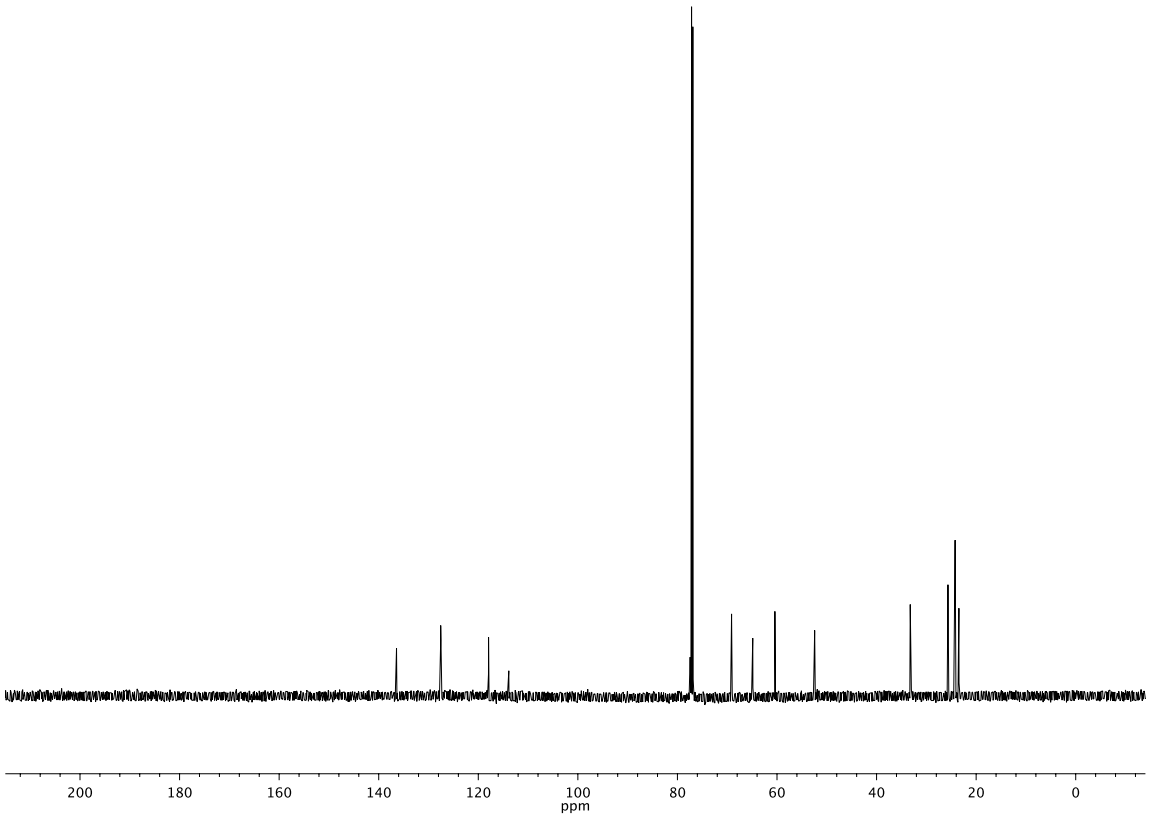


Figure A8.33. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **170e**.

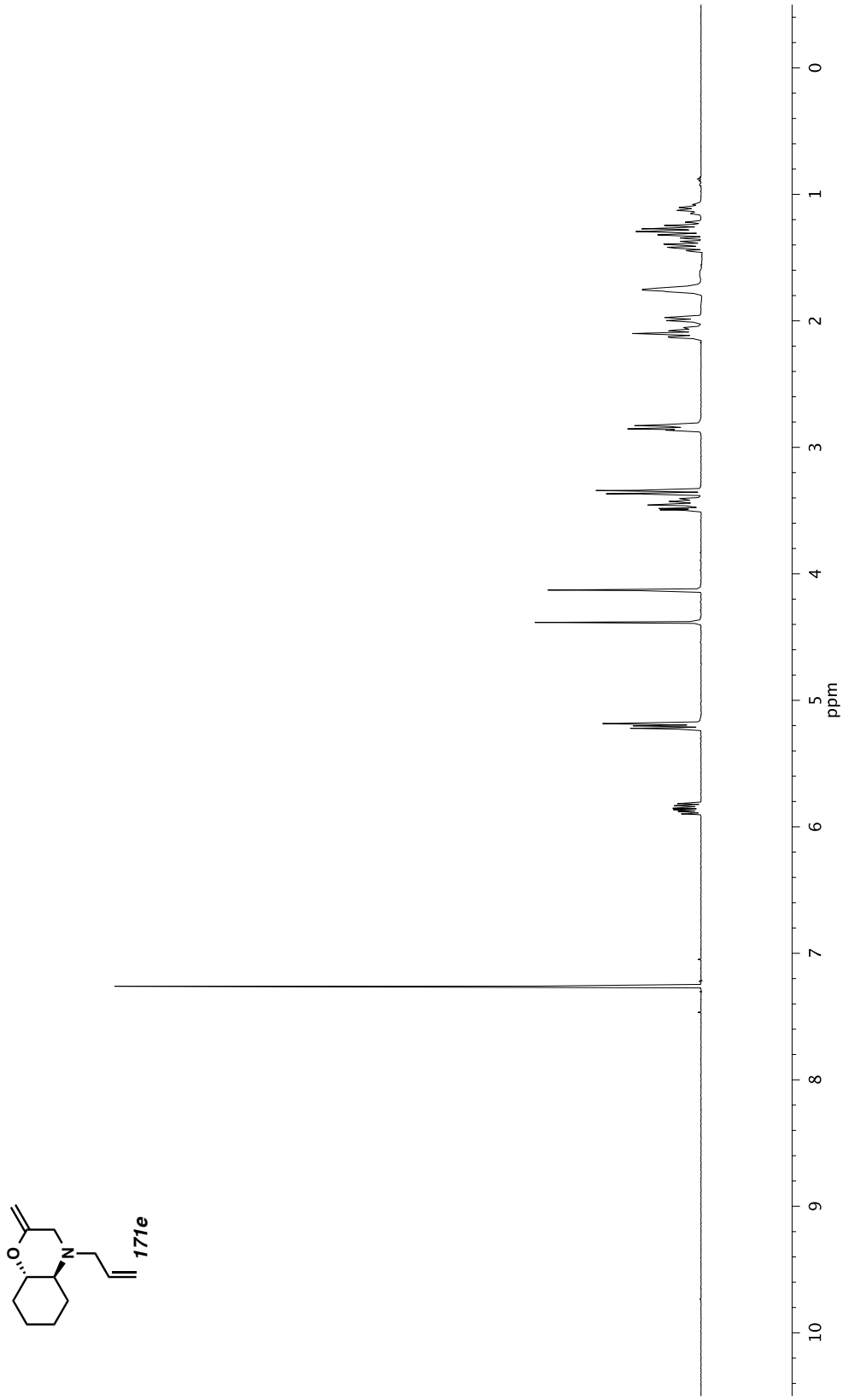


Figure A8.34. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **171e**.

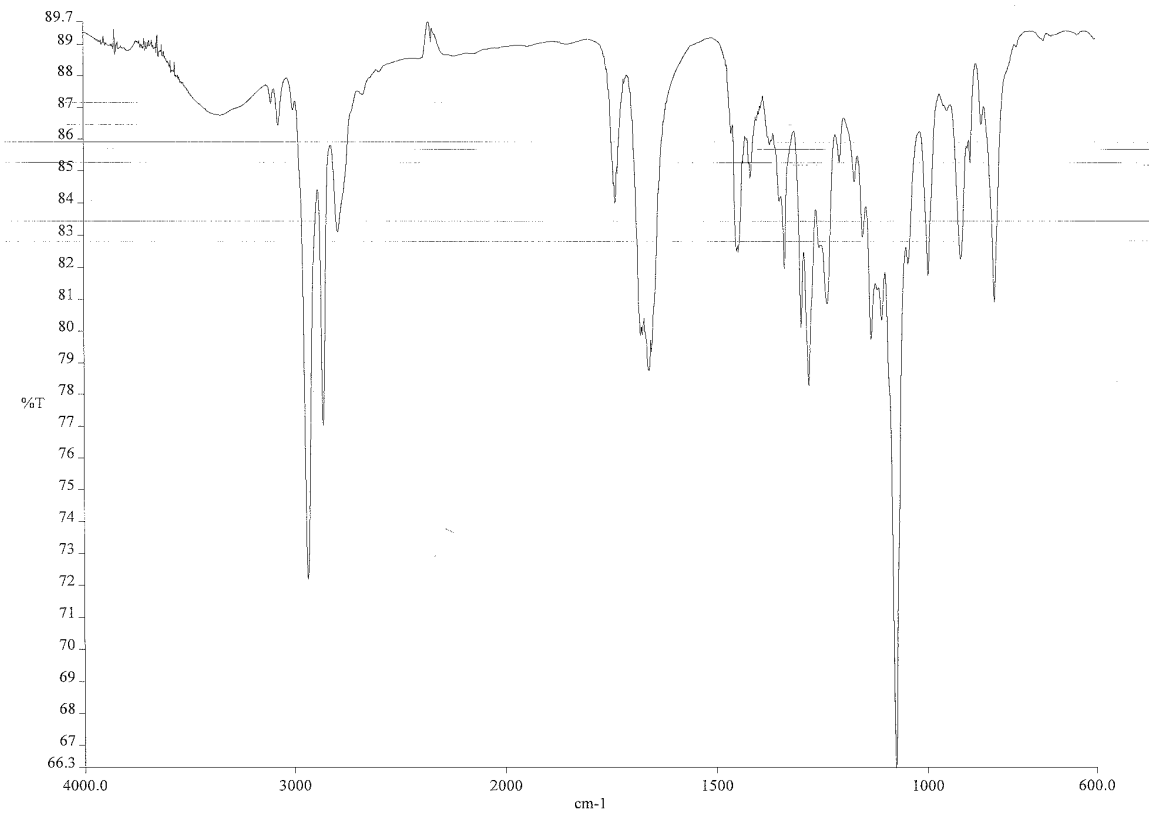


Figure A8.35. Infrared spectrum (Thin Film, NaCl) of compound **171e**.

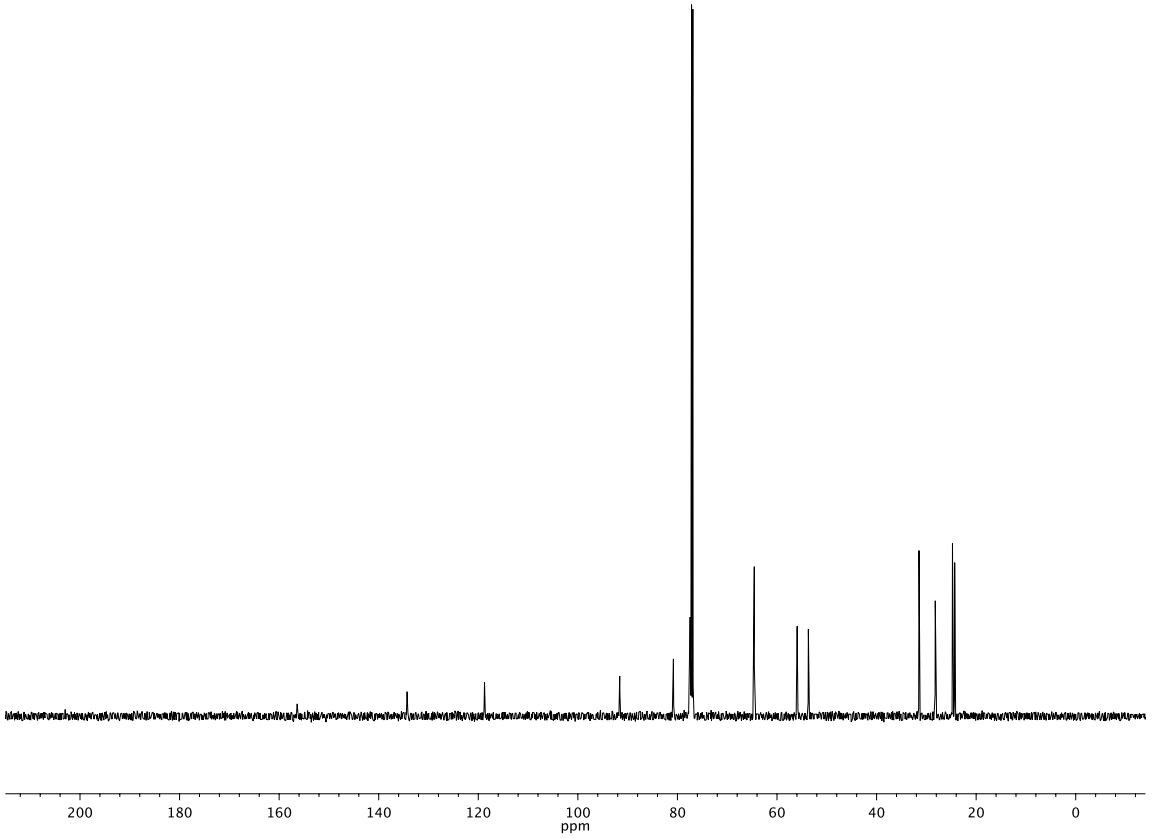


Figure A8.36. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **171e**.

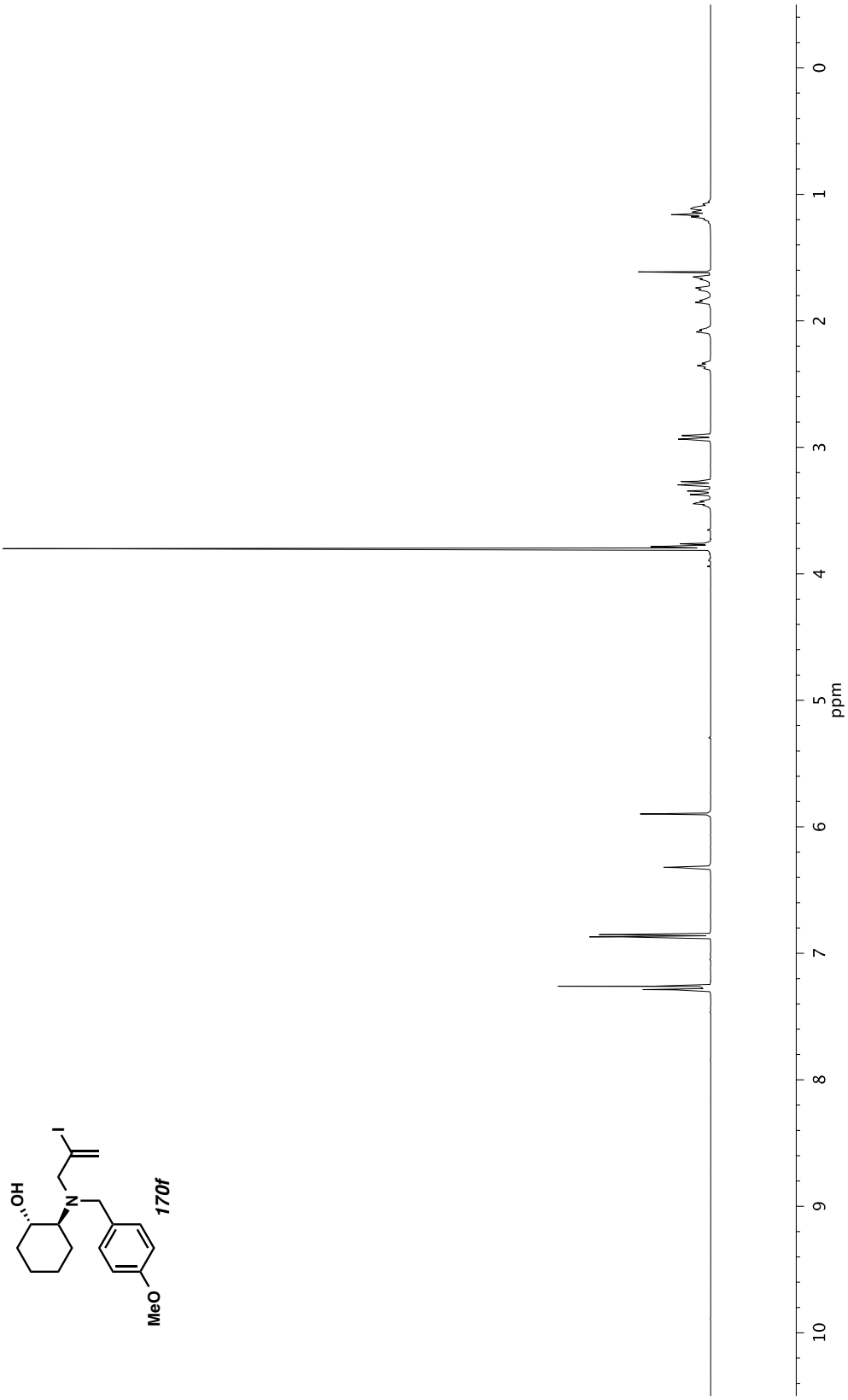


Figure A8.37. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **170f**.

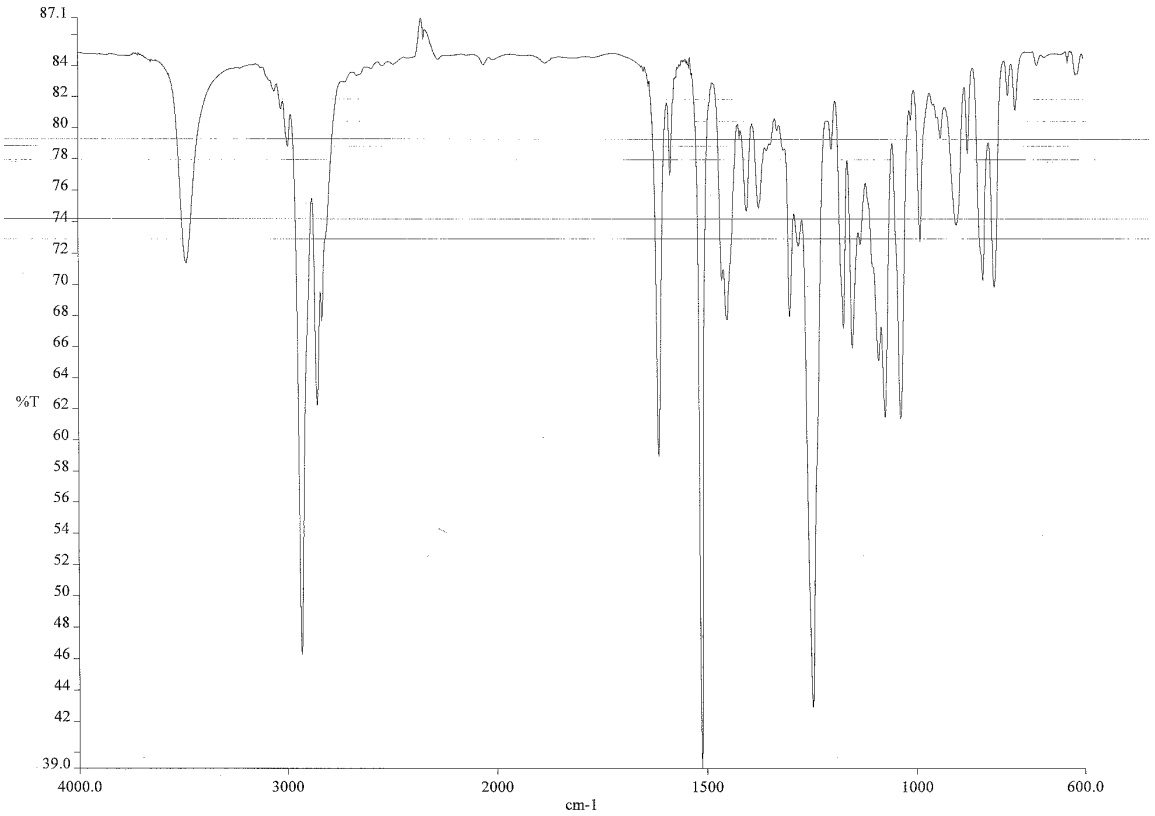


Figure A8.38. Infrared spectrum (Thin Film, NaCl) of compound **170f**.

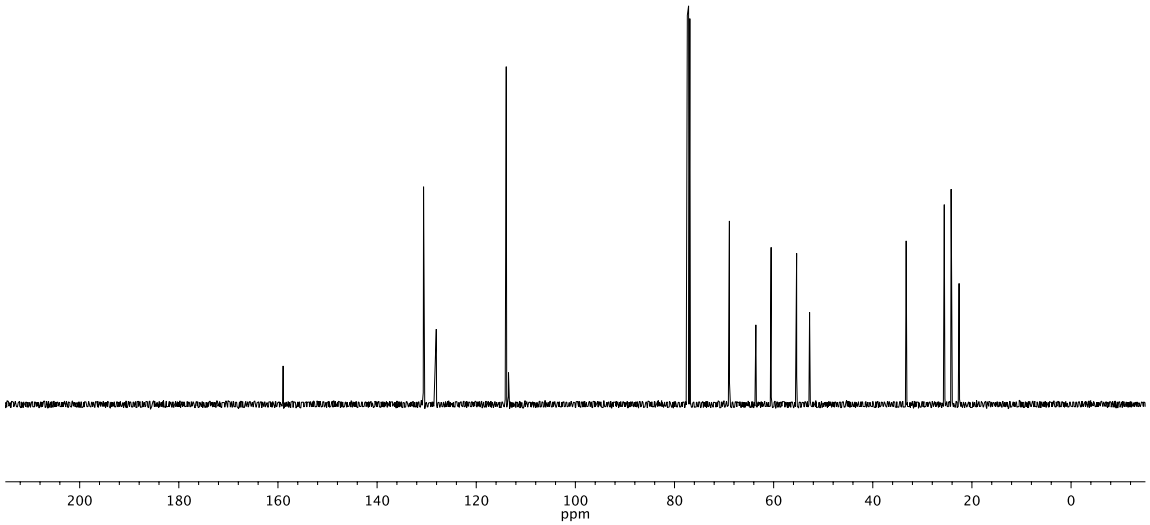


Figure A8.39. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **170f**.

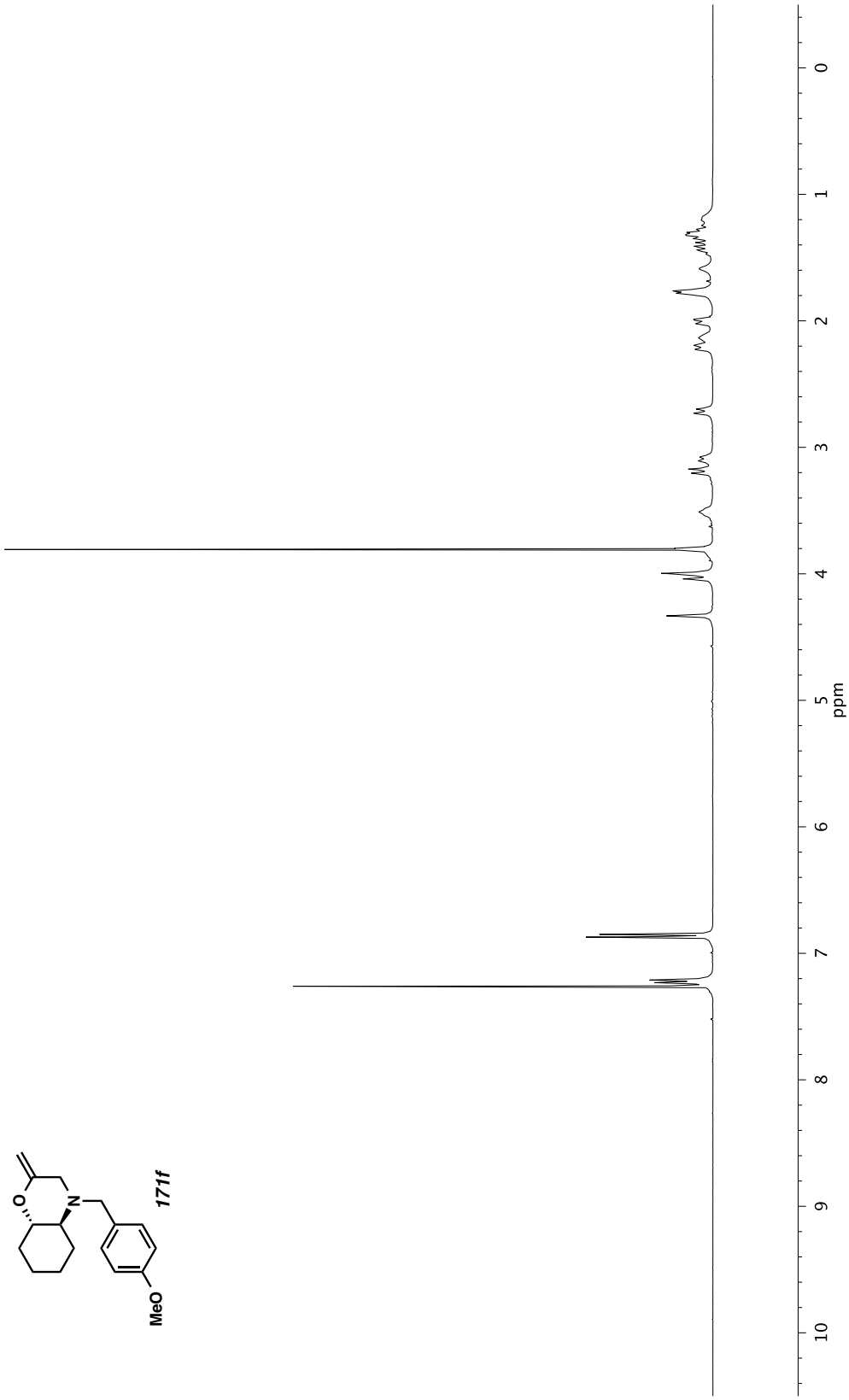


Figure A8.40. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **171f**.

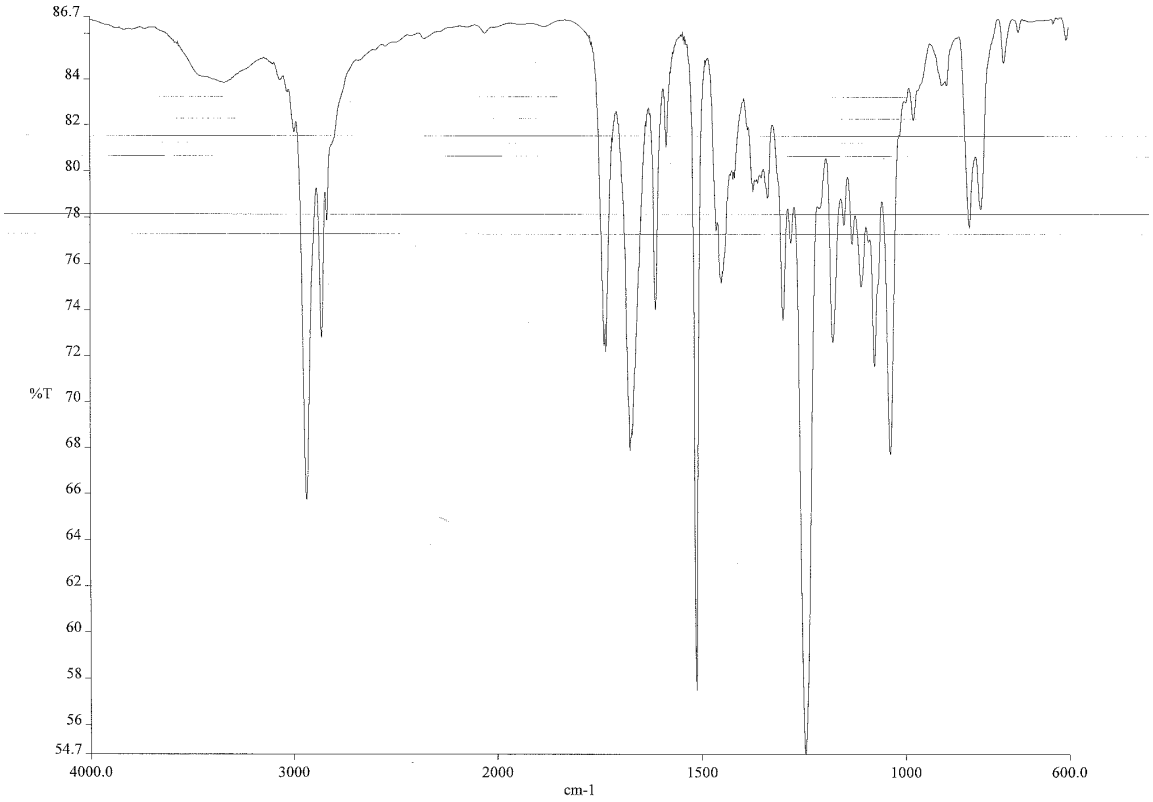


Figure A8.41. Infrared spectrum (Thin Film, NaCl) of compound **171f**.

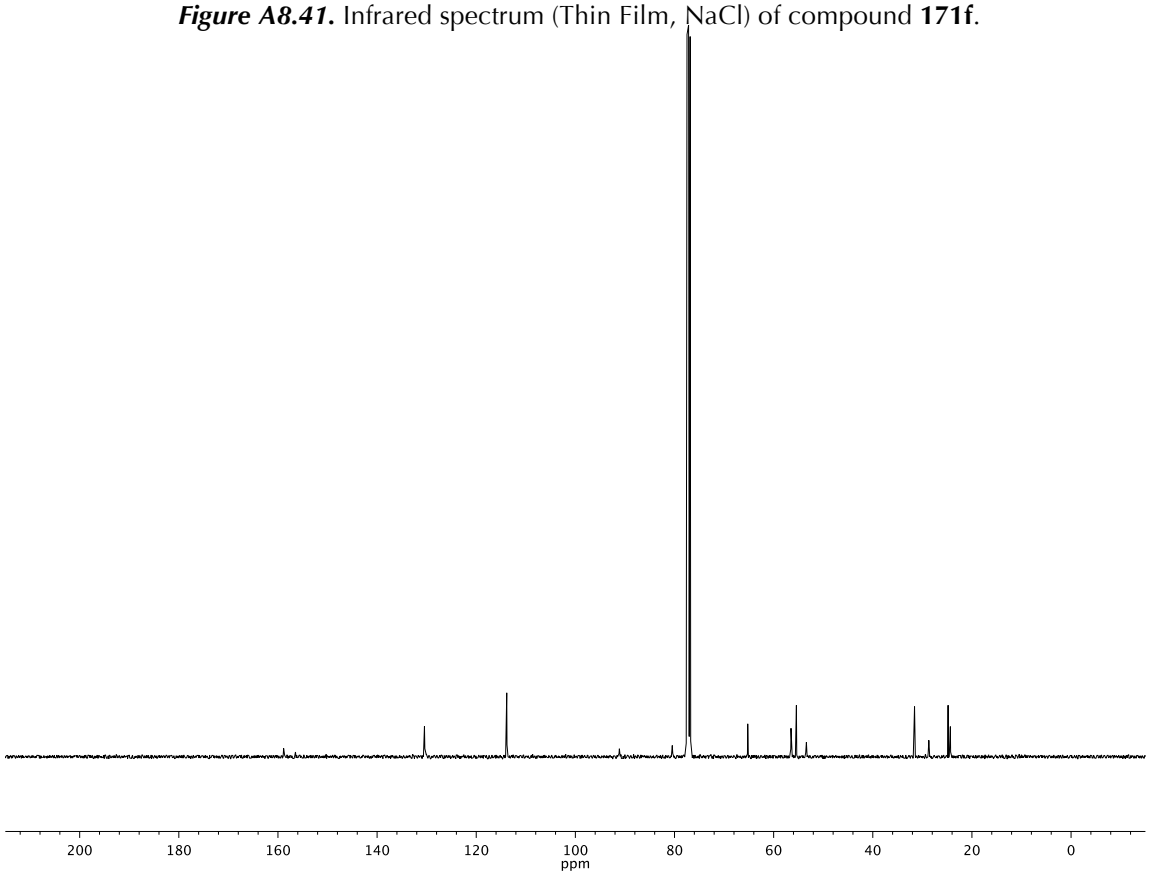


Figure A8.42. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **171f**.

Figure A8.43. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **170g**.

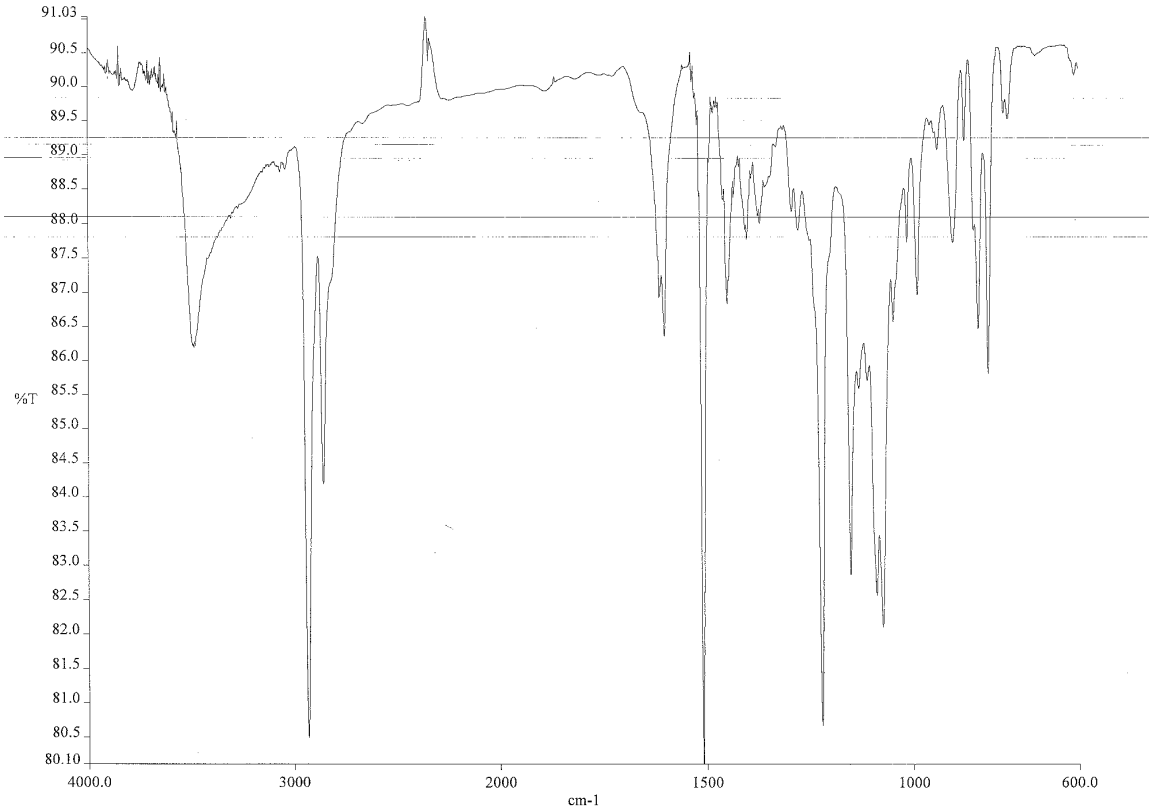


Figure A8.44. Infrared spectrum (Thin Film, NaCl) of compound **170g**.

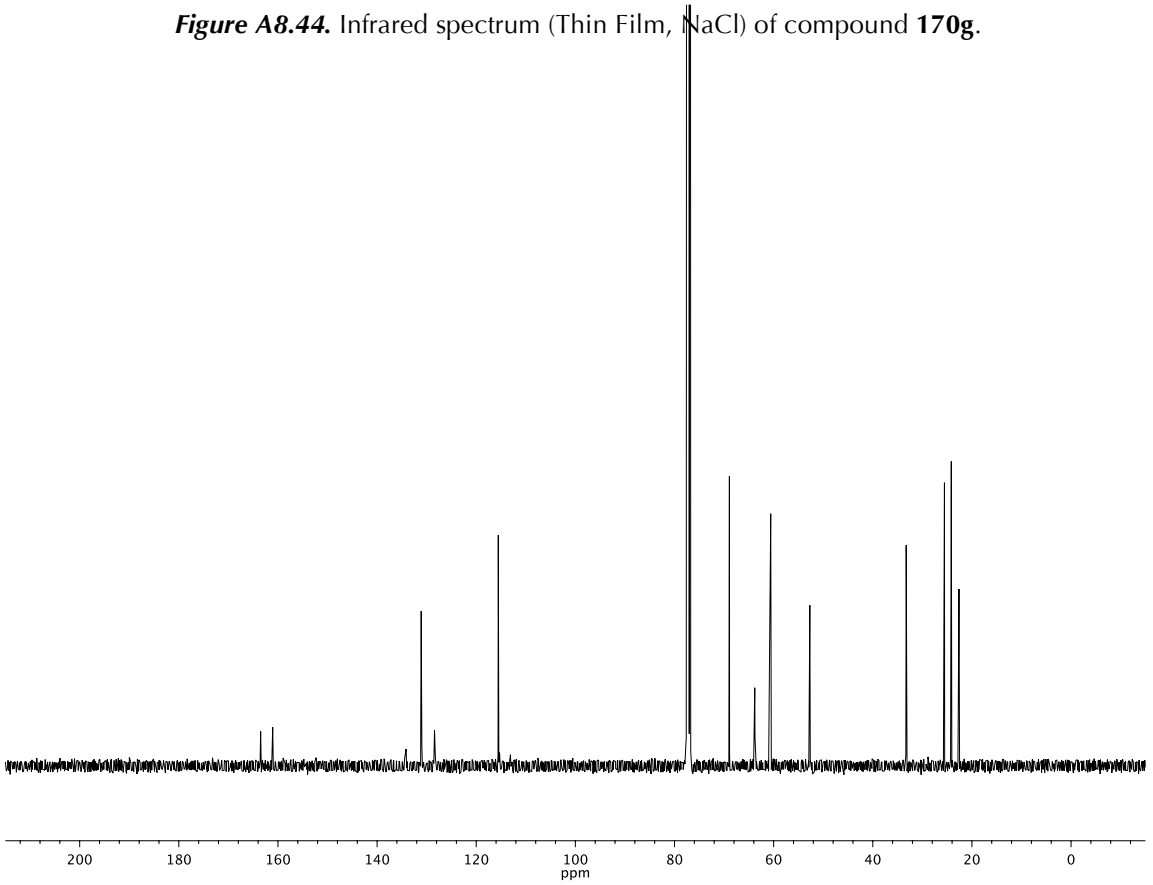


Figure A8.45. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **170g**.

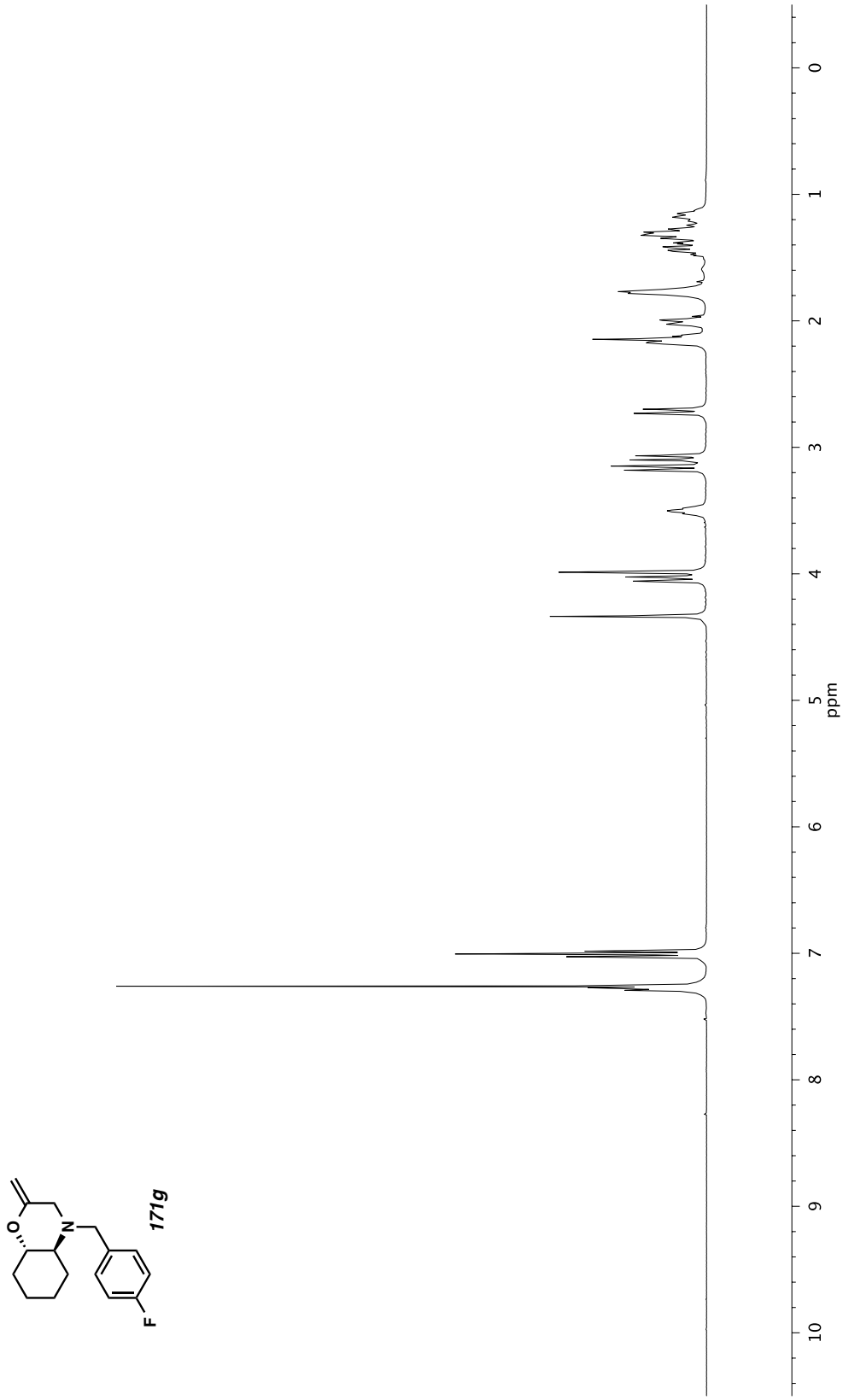


Figure A8.46. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **171g**.

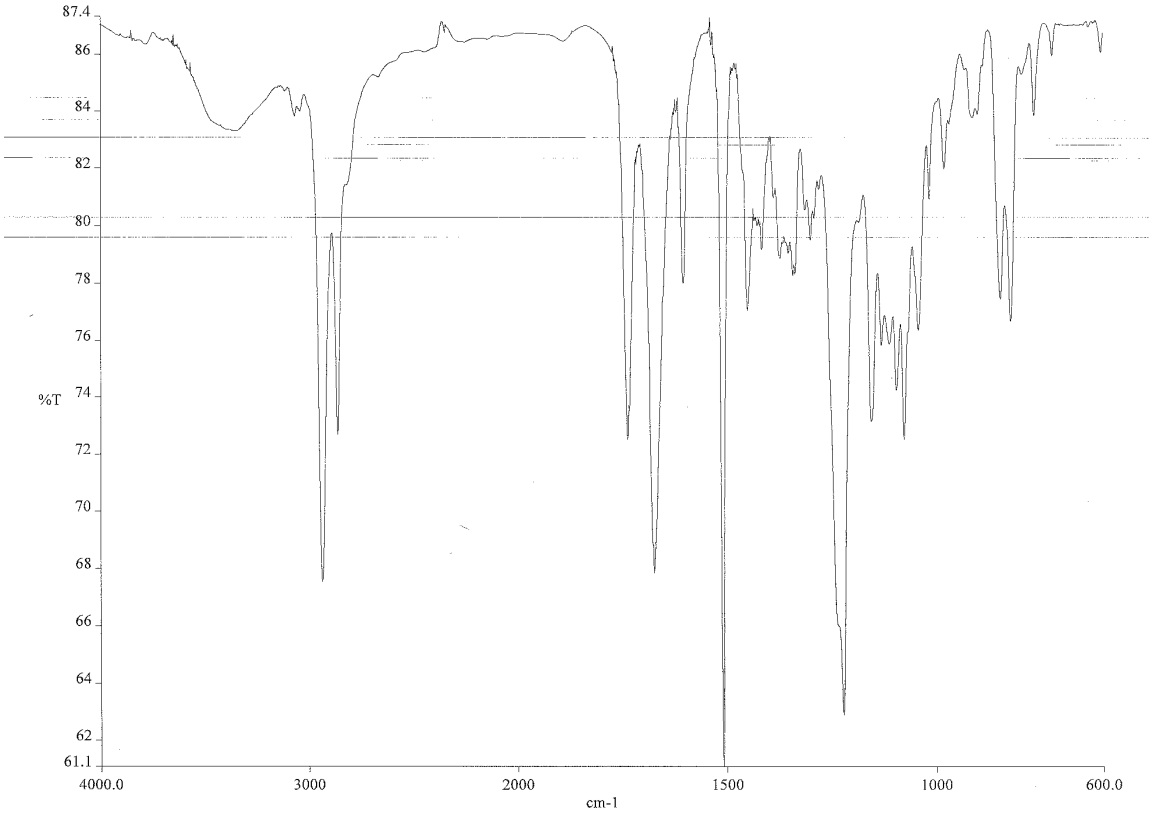


Figure A8.47. Infrared spectrum (Thin Film, NaCl) of compound **171g**.

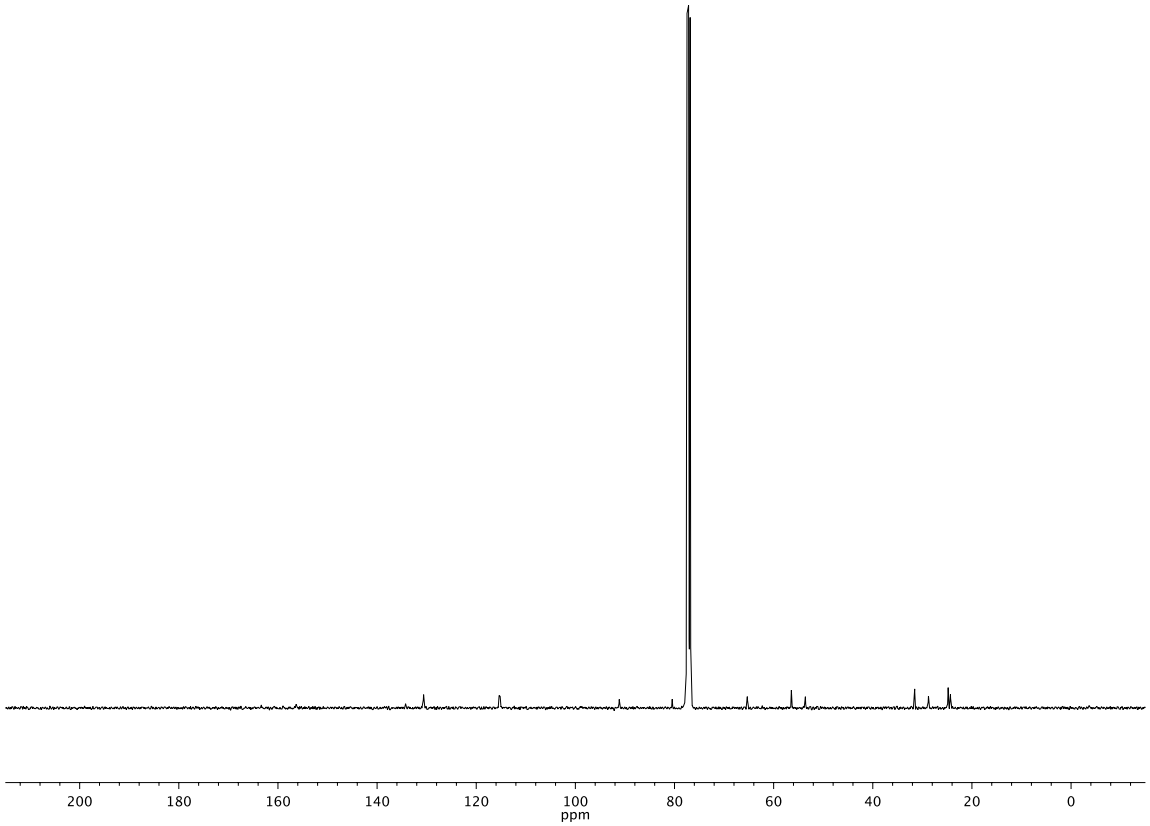


Figure A8.48. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **171g**.

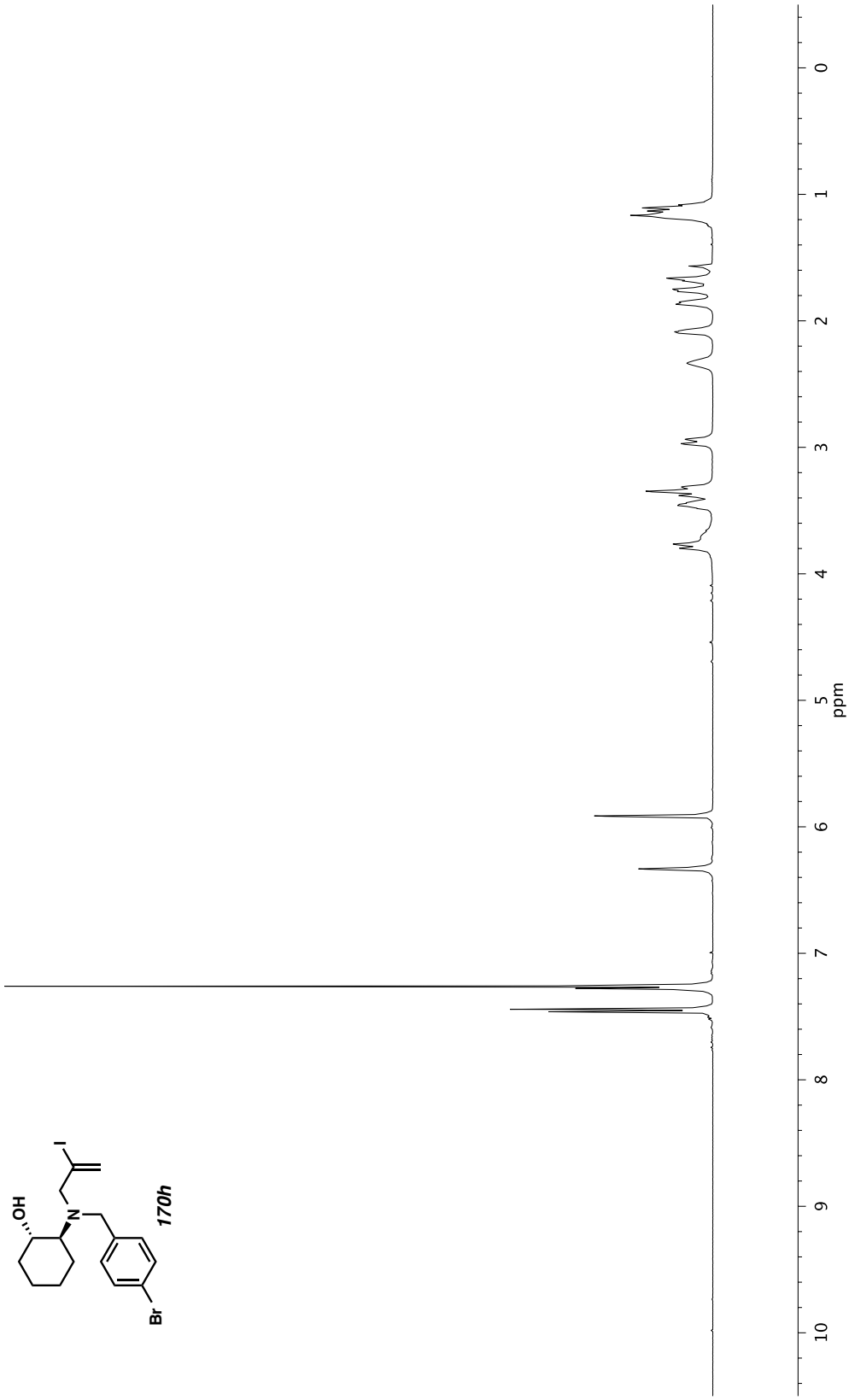


Figure A8.49. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **170h**.

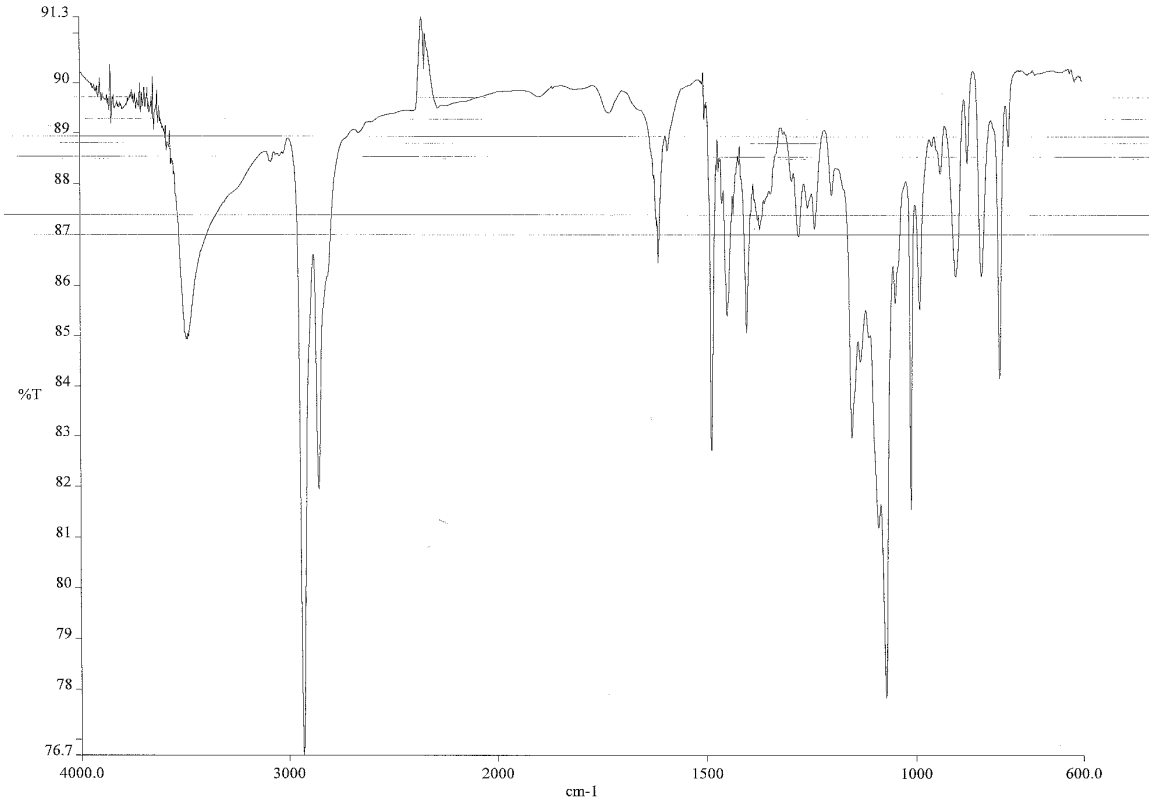


Figure A8.50. Infrared spectrum (Thin Film, NaCl) of compound **170h**.

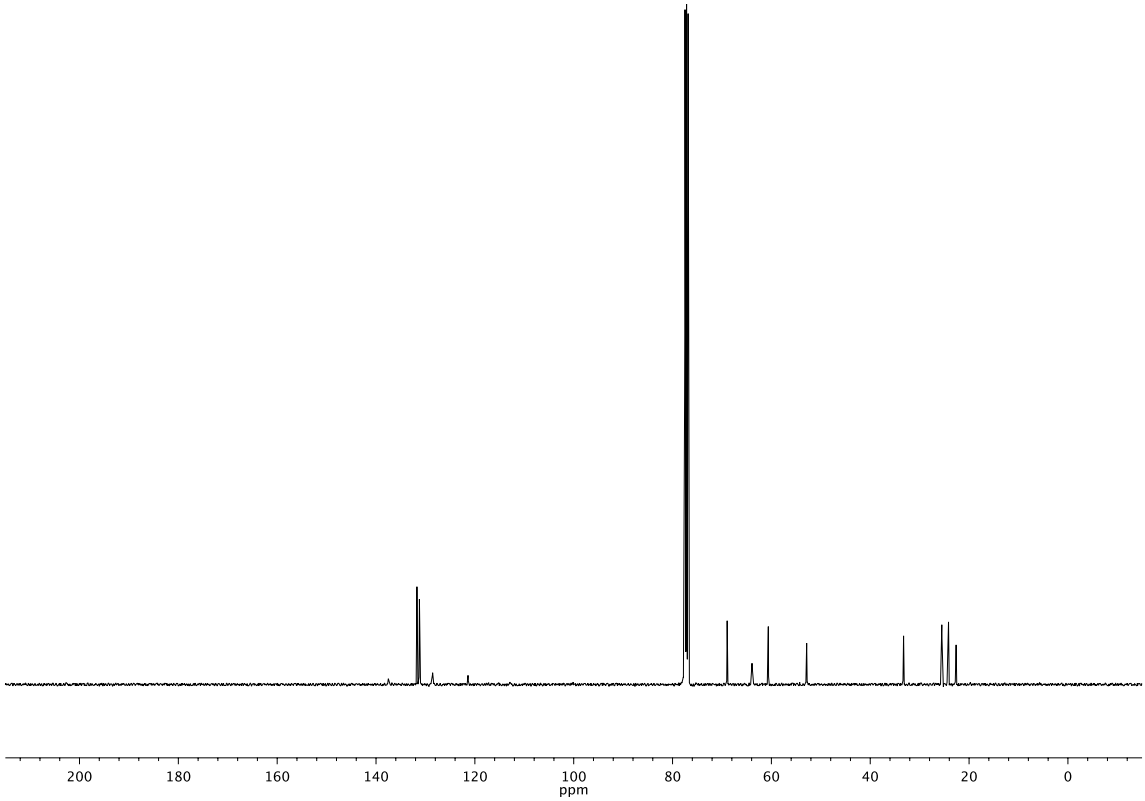


Figure A8.51. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **170h**.

Figure A8.52. ^{1}H NMR (500 MHz, CD_2Cl_2) of compound **171h**.

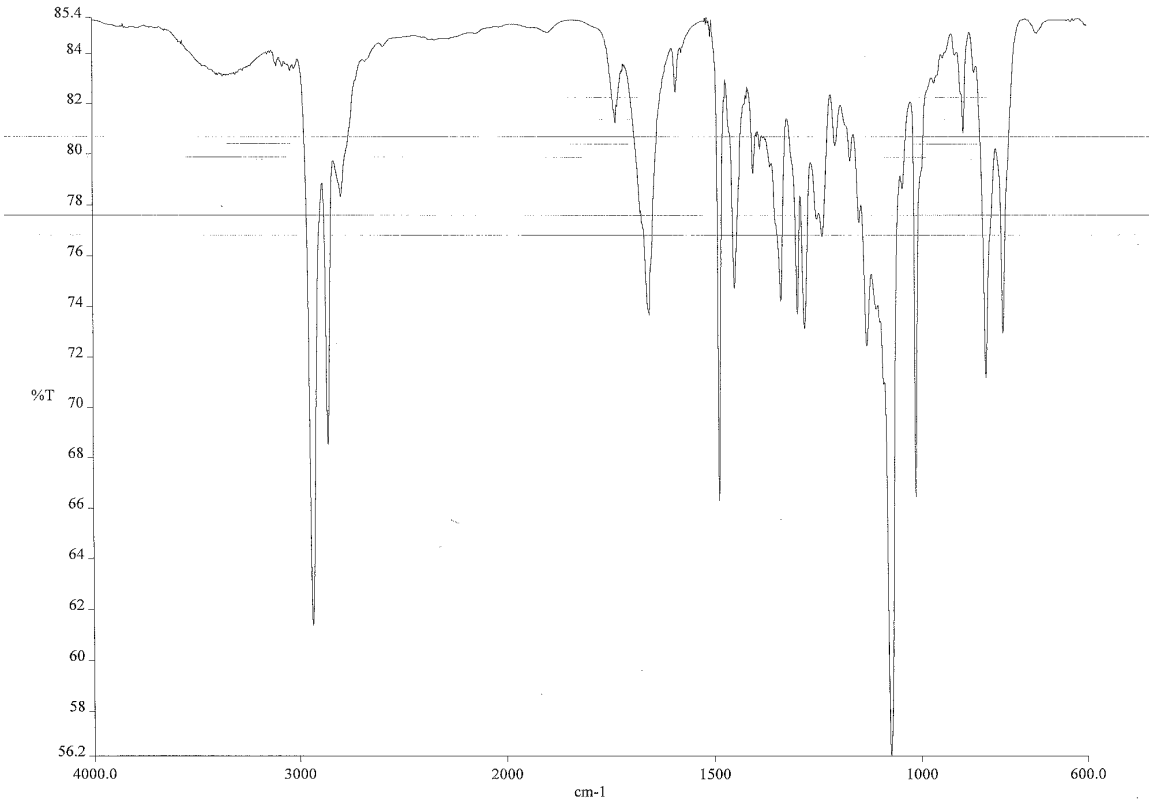


Figure A8.53. Infrared spectrum (Thin Film, NaCl) of compound **171h**.

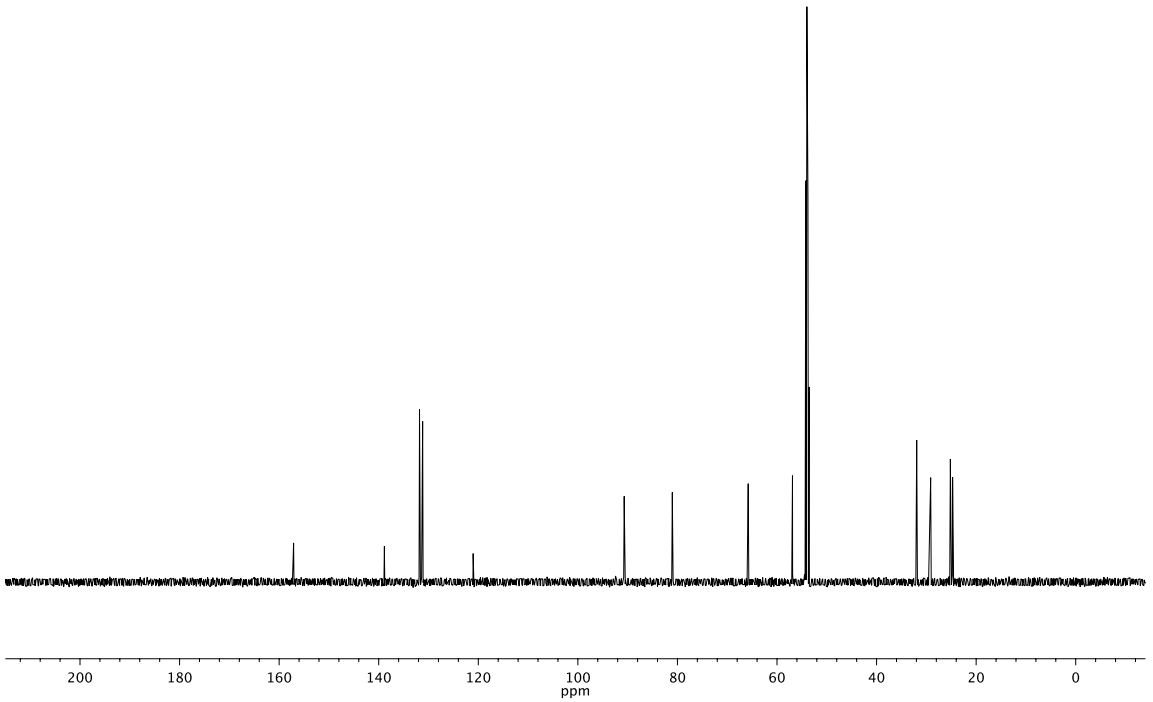


Figure A8.54. ^{13}C NMR (126 MHz, CD_2Cl_2) of compound **171h**.

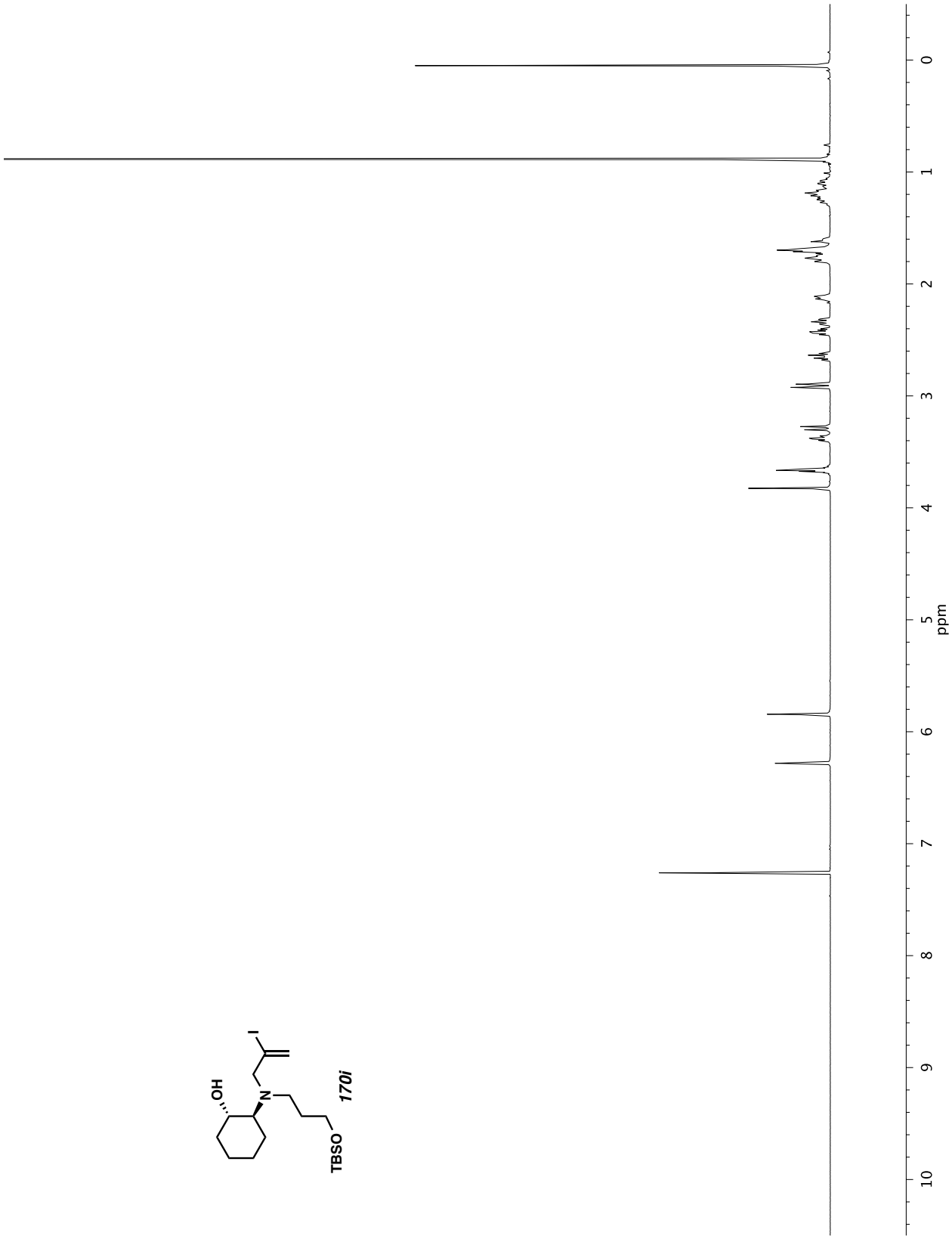


Figure A8.55. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **170i**.

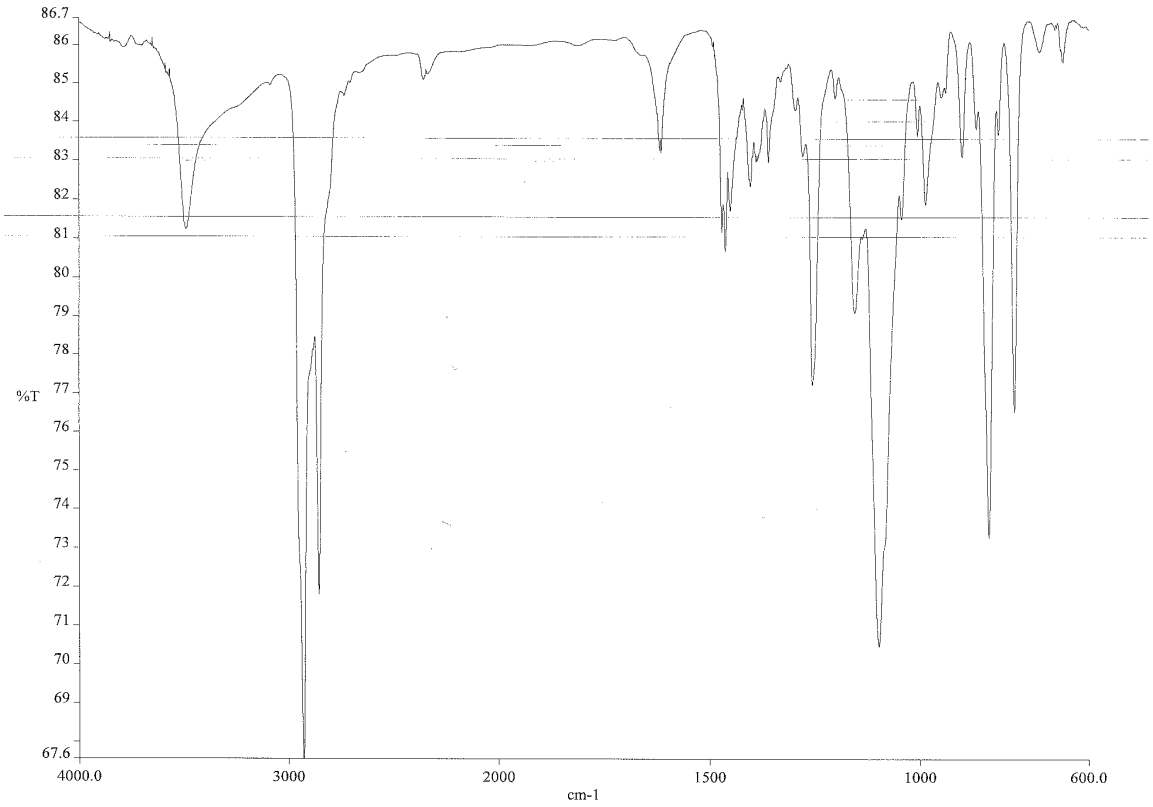


Figure A8.56. Infrared spectrum (Thin Film, NaCl) of compound **170i**.

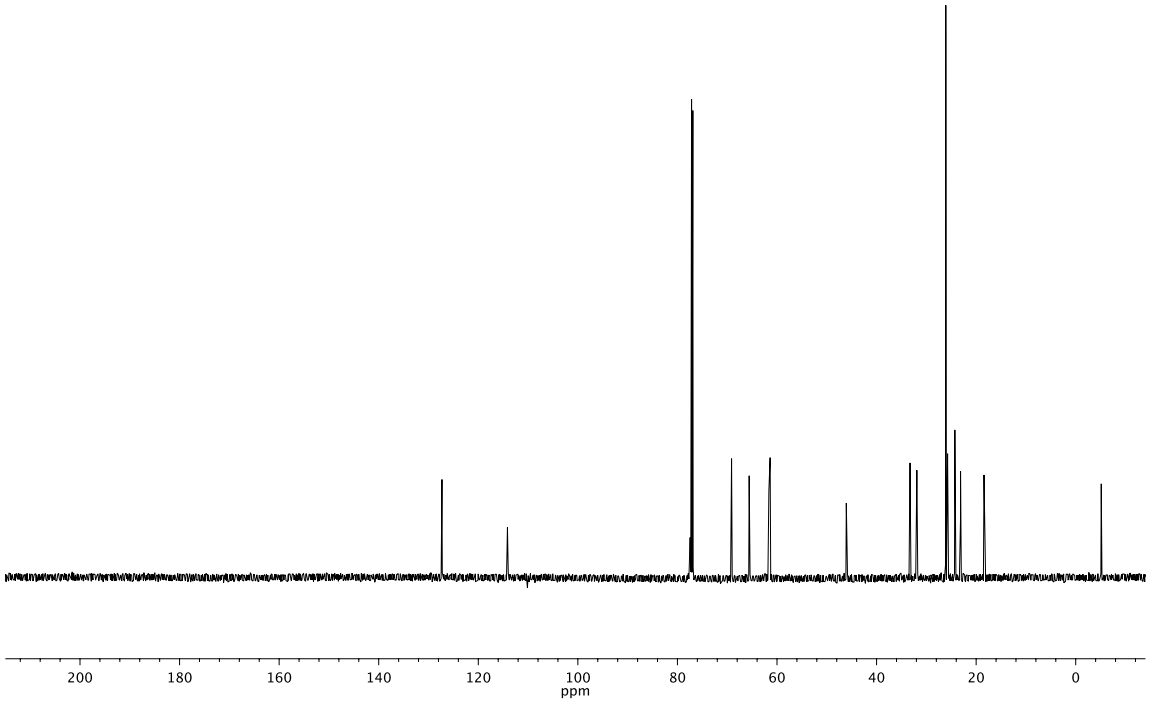


Figure A8.57. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **170i**.

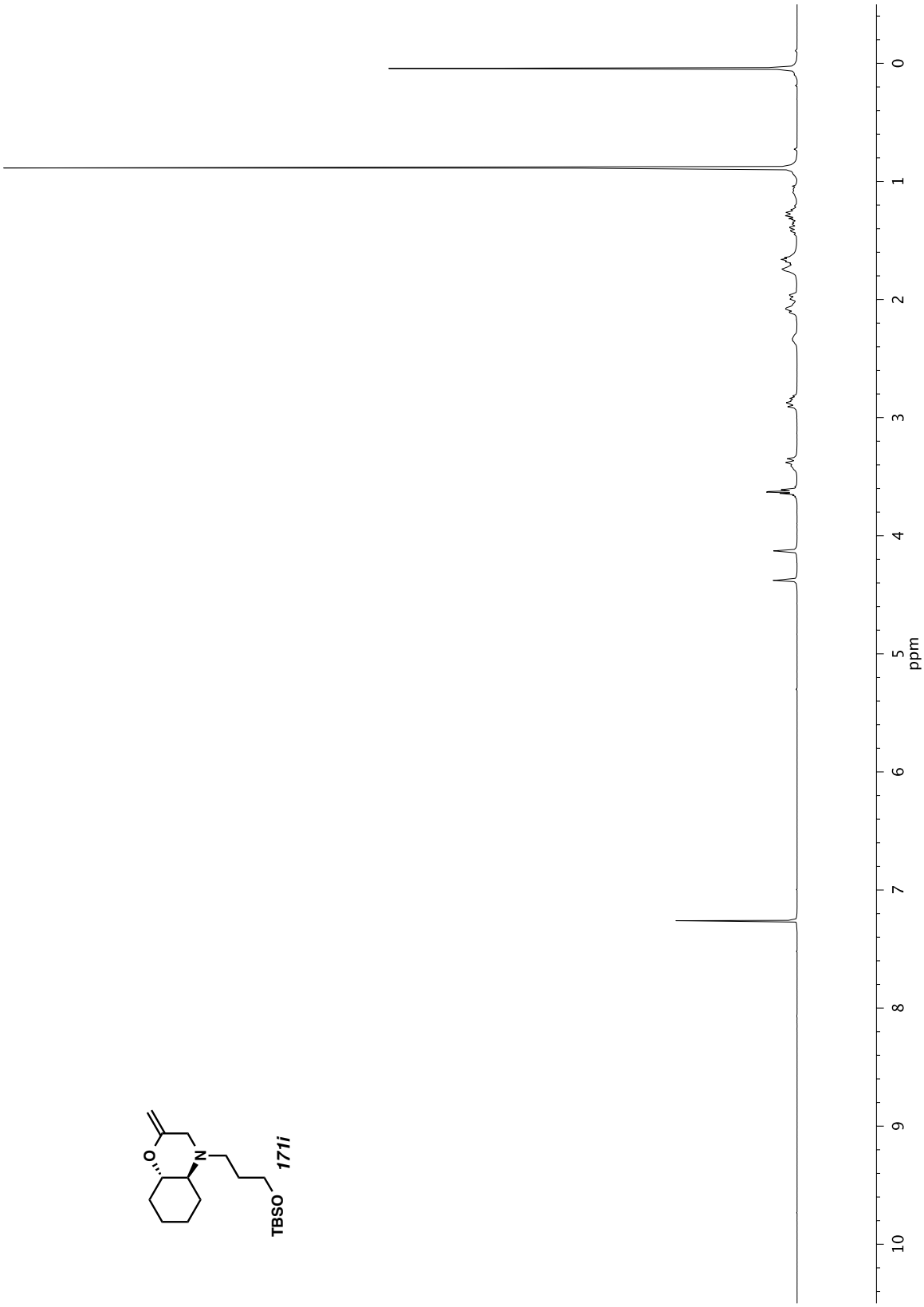


Figure A8.58. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **171i**.

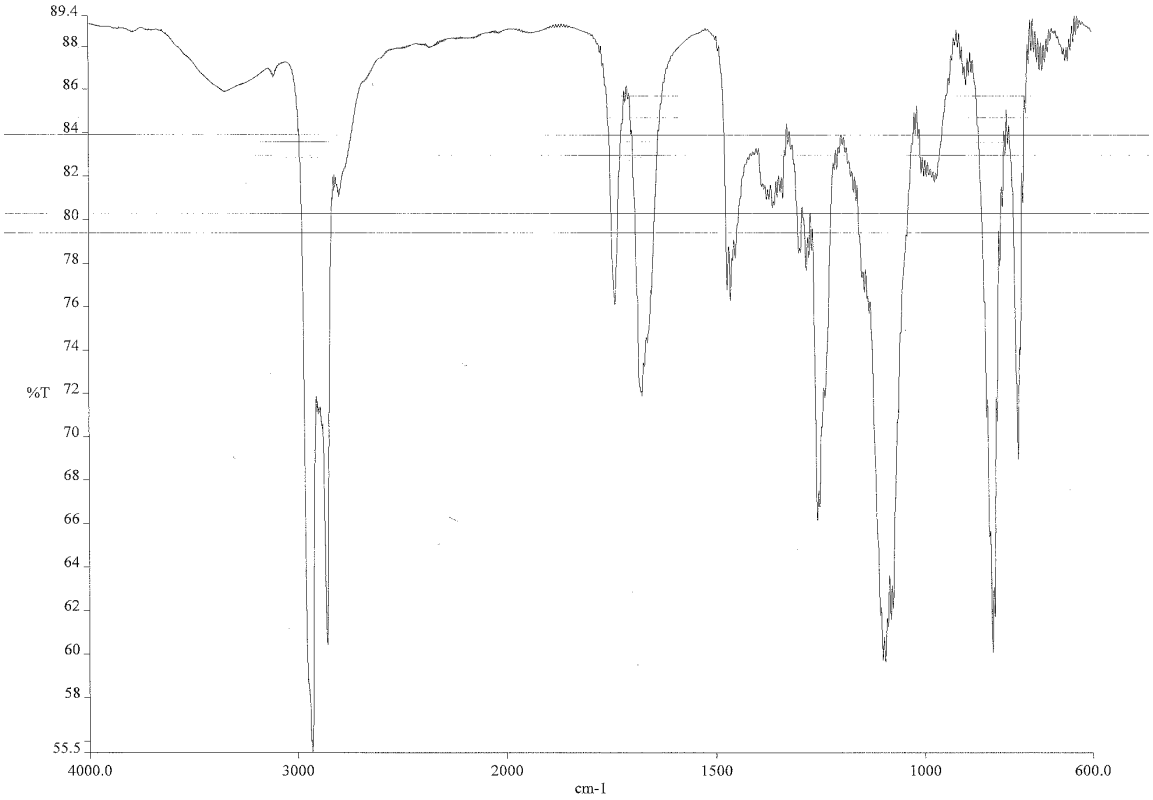


Figure A8.59. Infrared spectrum (Thin Film, NaCl) of compound **171i**.

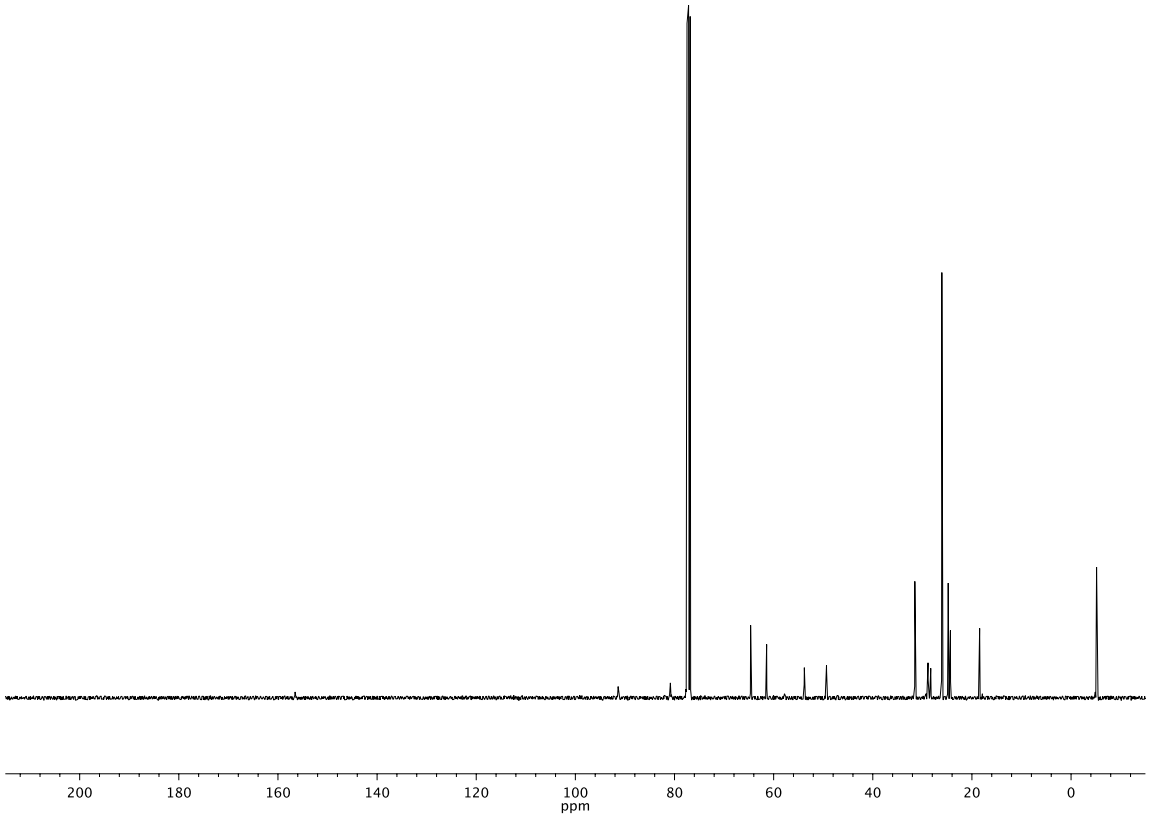


Figure A8.60. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **171i**.

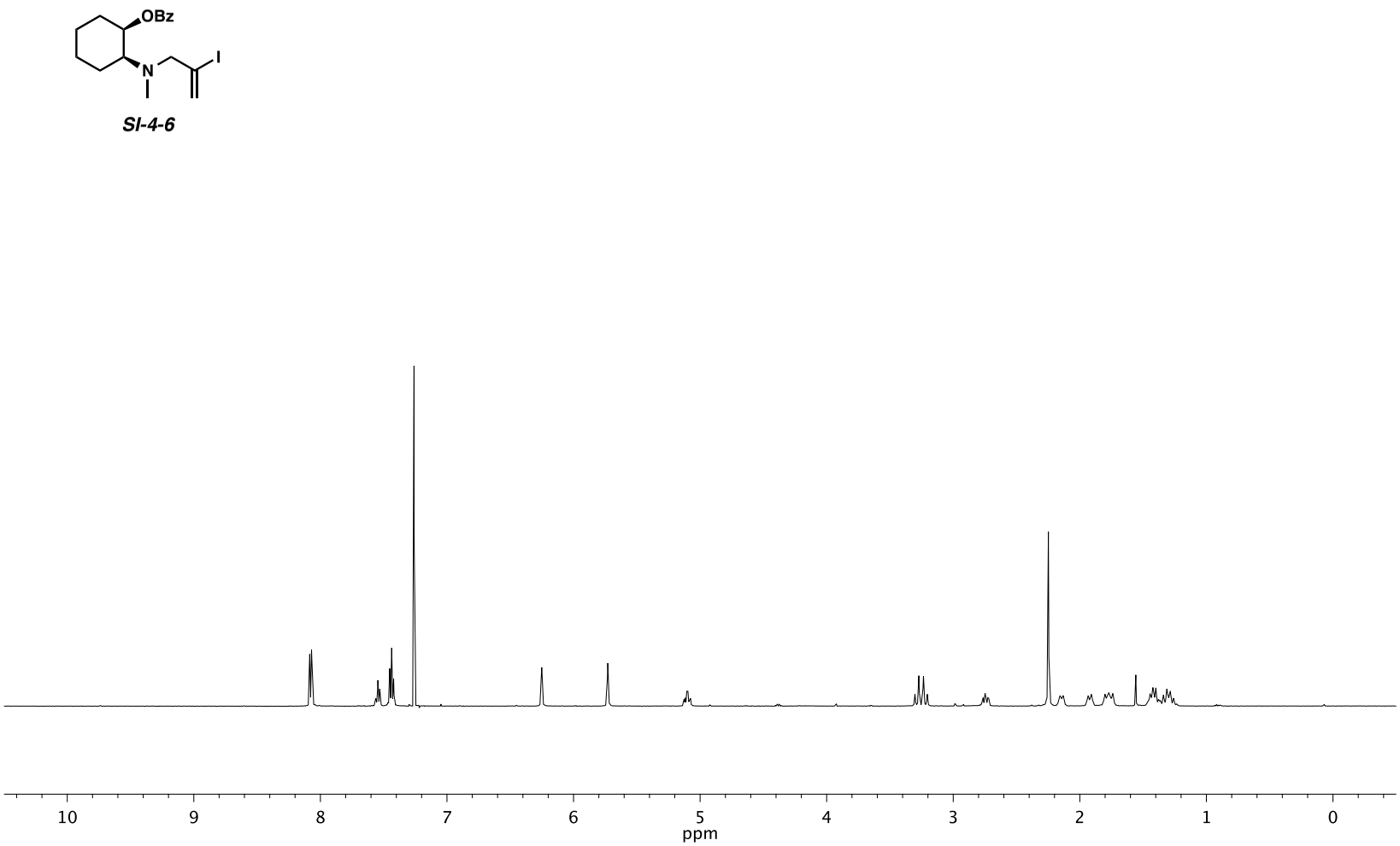


Figure A8.61. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **SI-4-6**.

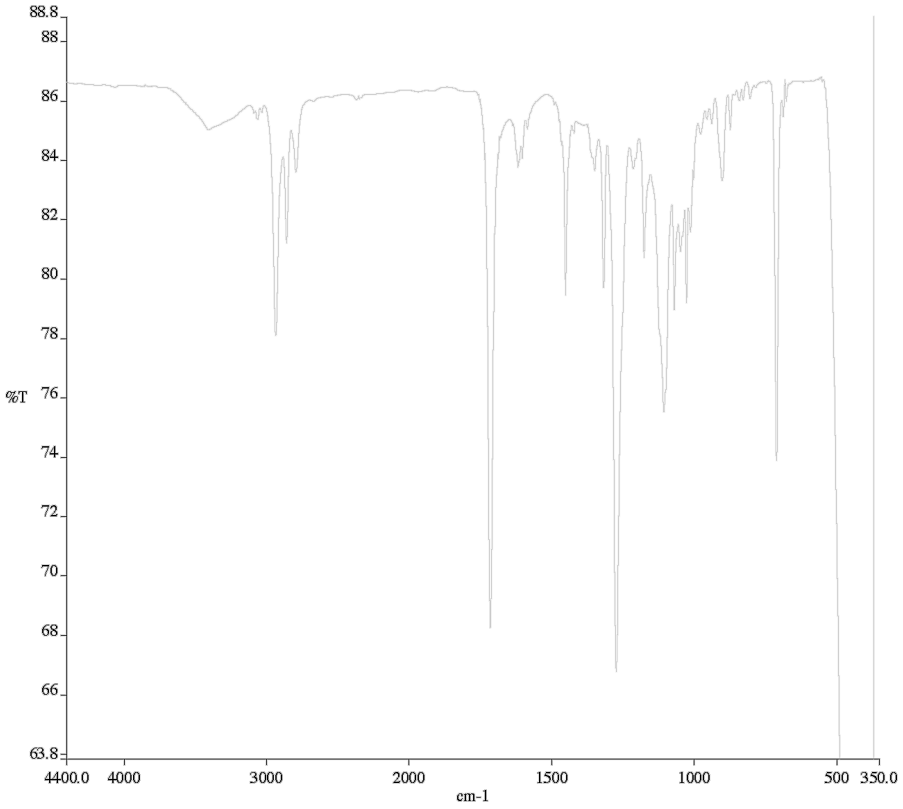


Figure A8.62. Infrared spectrum (Thin Film, NaCl) of compound **SI-4-6**.

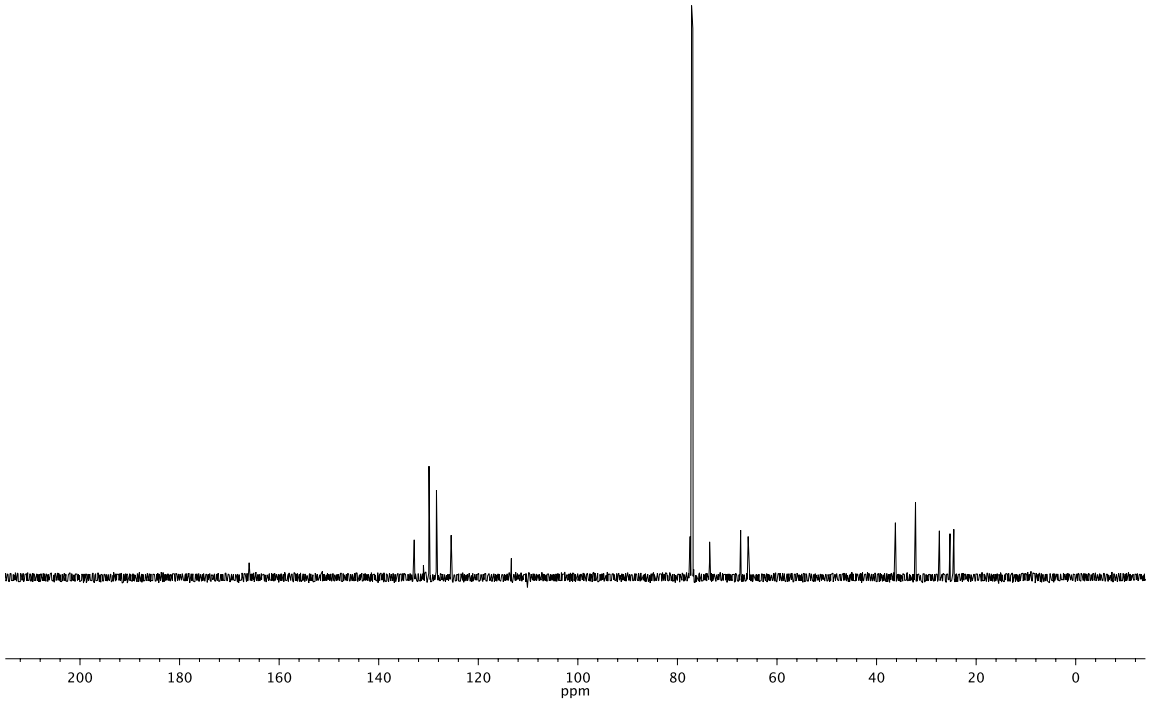


Figure A8.63. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **SI-4-6**.

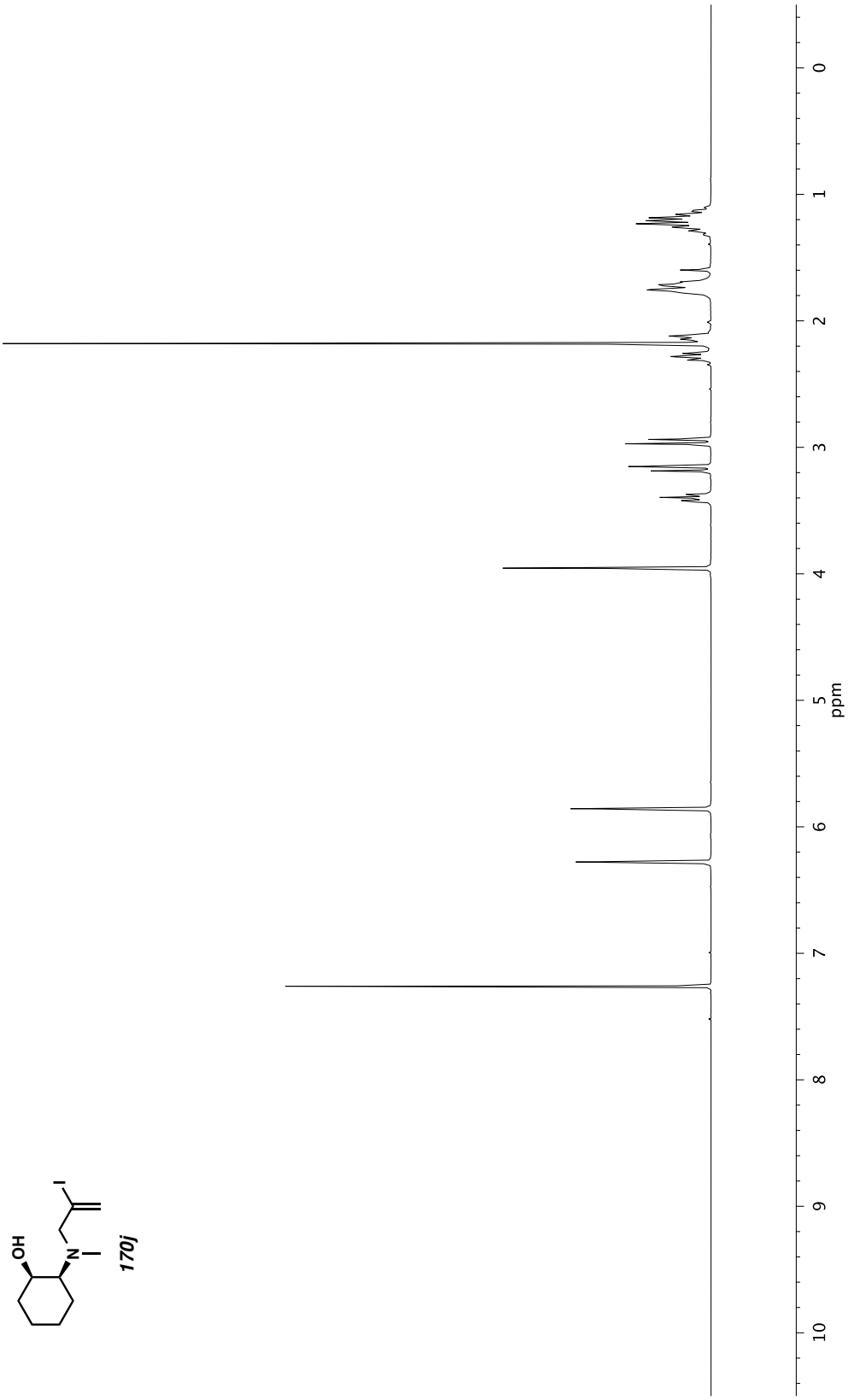


Figure A8.64. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **170j**.

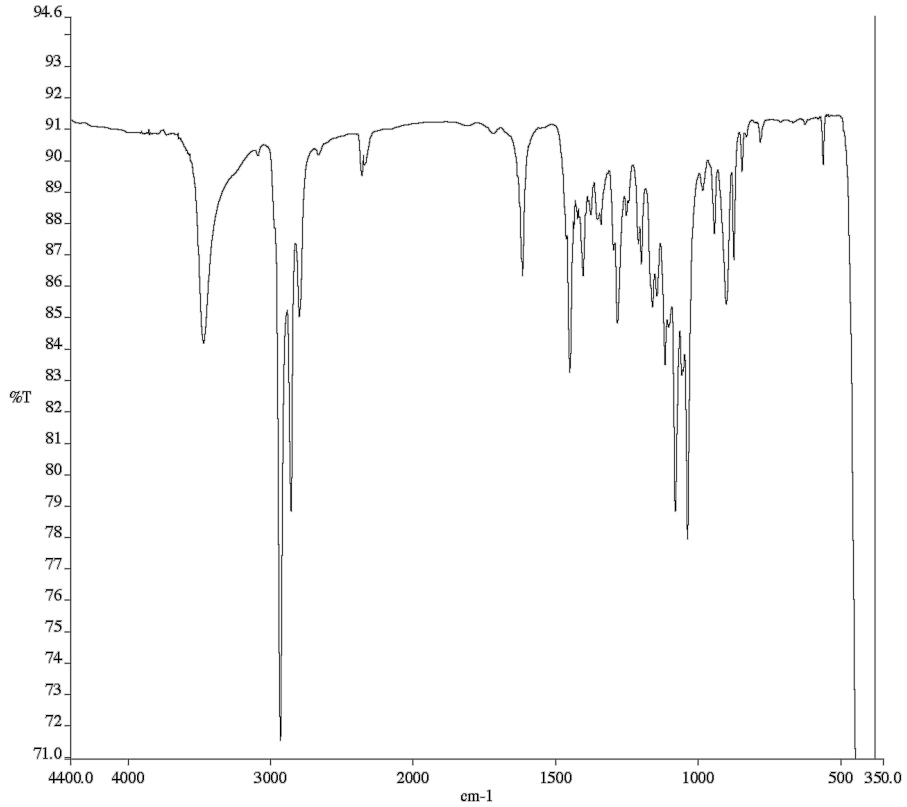


Figure A8.65. Infrared spectrum (Thin Film, NaCl) of compound **170j**.

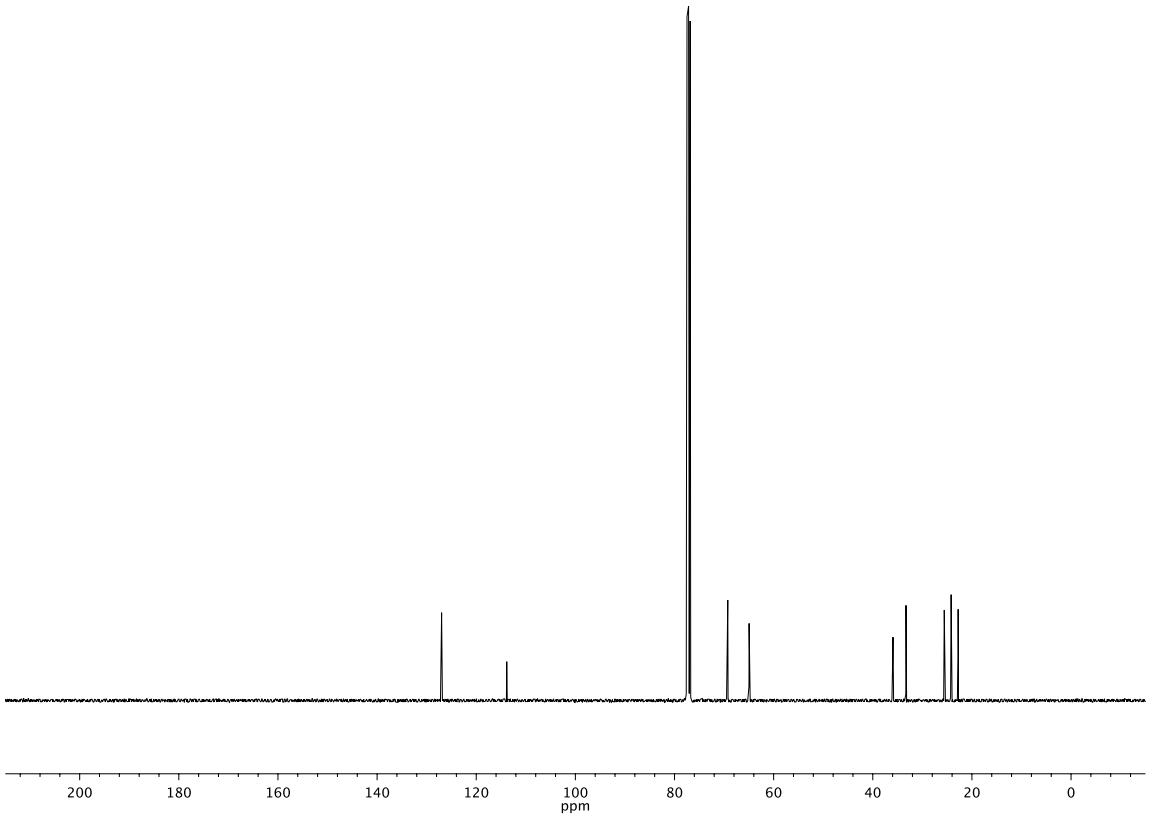
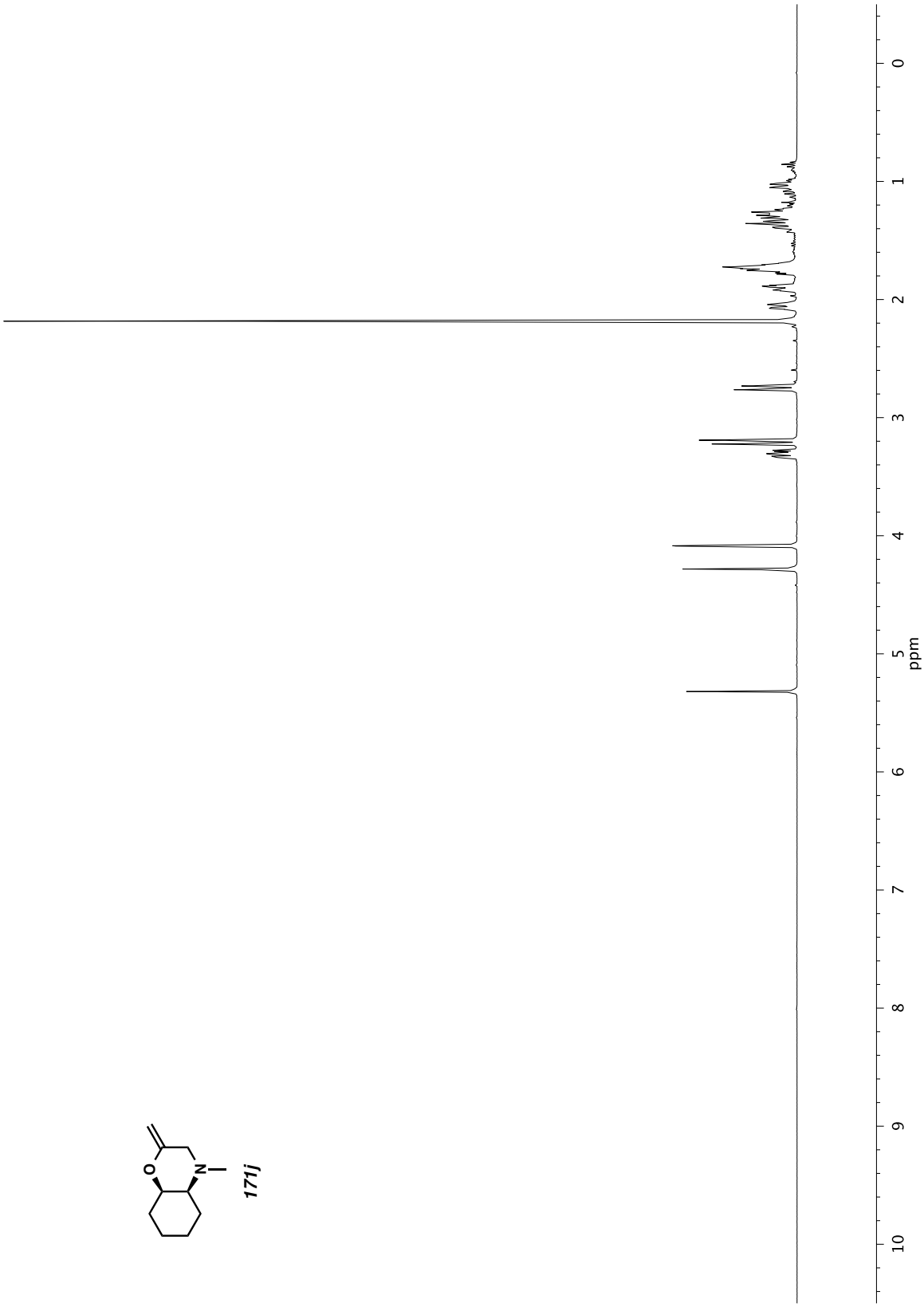


Figure A8.66. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **170j**.



171j

Figure A8.67. ^{1}H NMR (400 MHz, CD_2Cl_2) of compound **171j**.

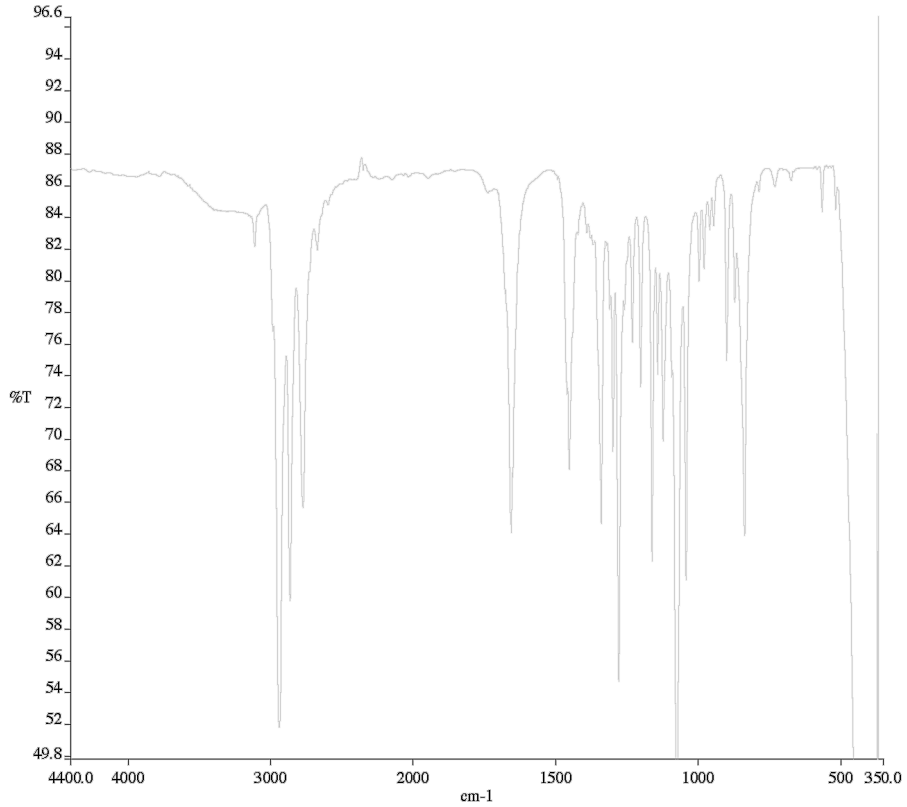


Figure A8.68. Infrared spectrum (Thin Film, NaCl) of compound **171j**.

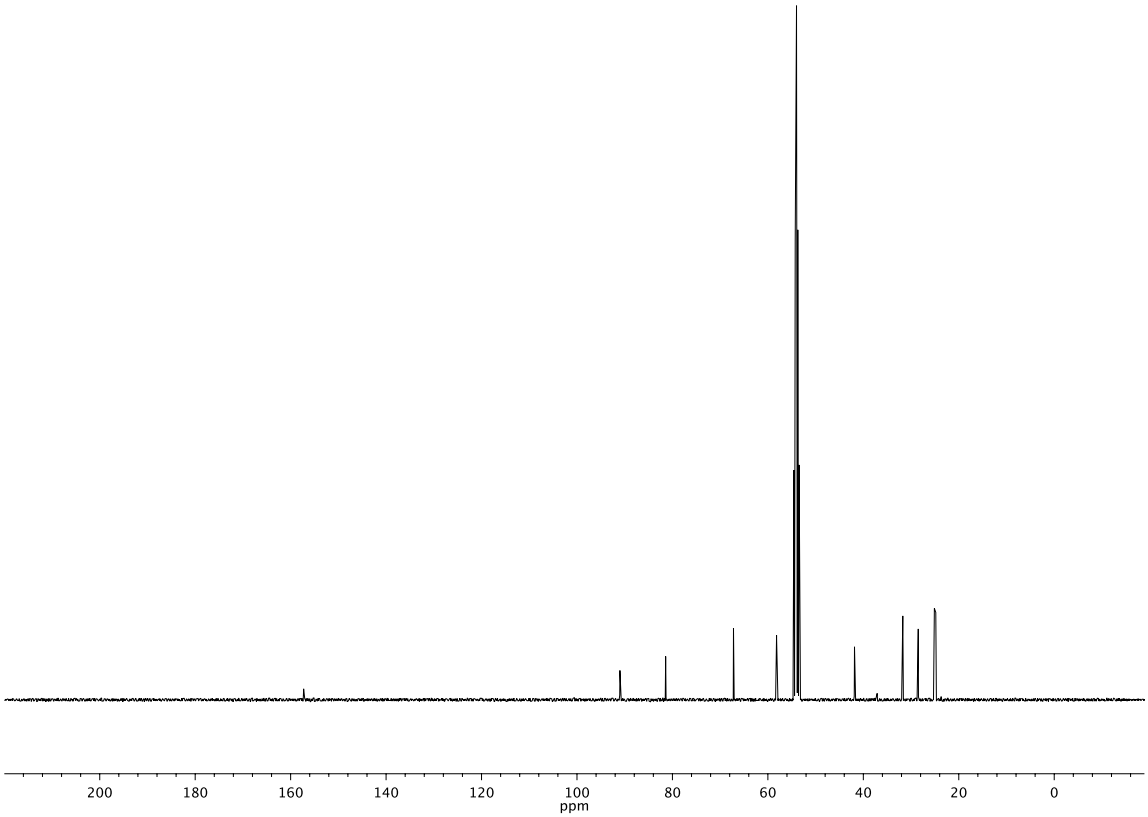


Figure A8.69. ^{13}C NMR (101 MHz, CD_2Cl_2) of compound **171j**.

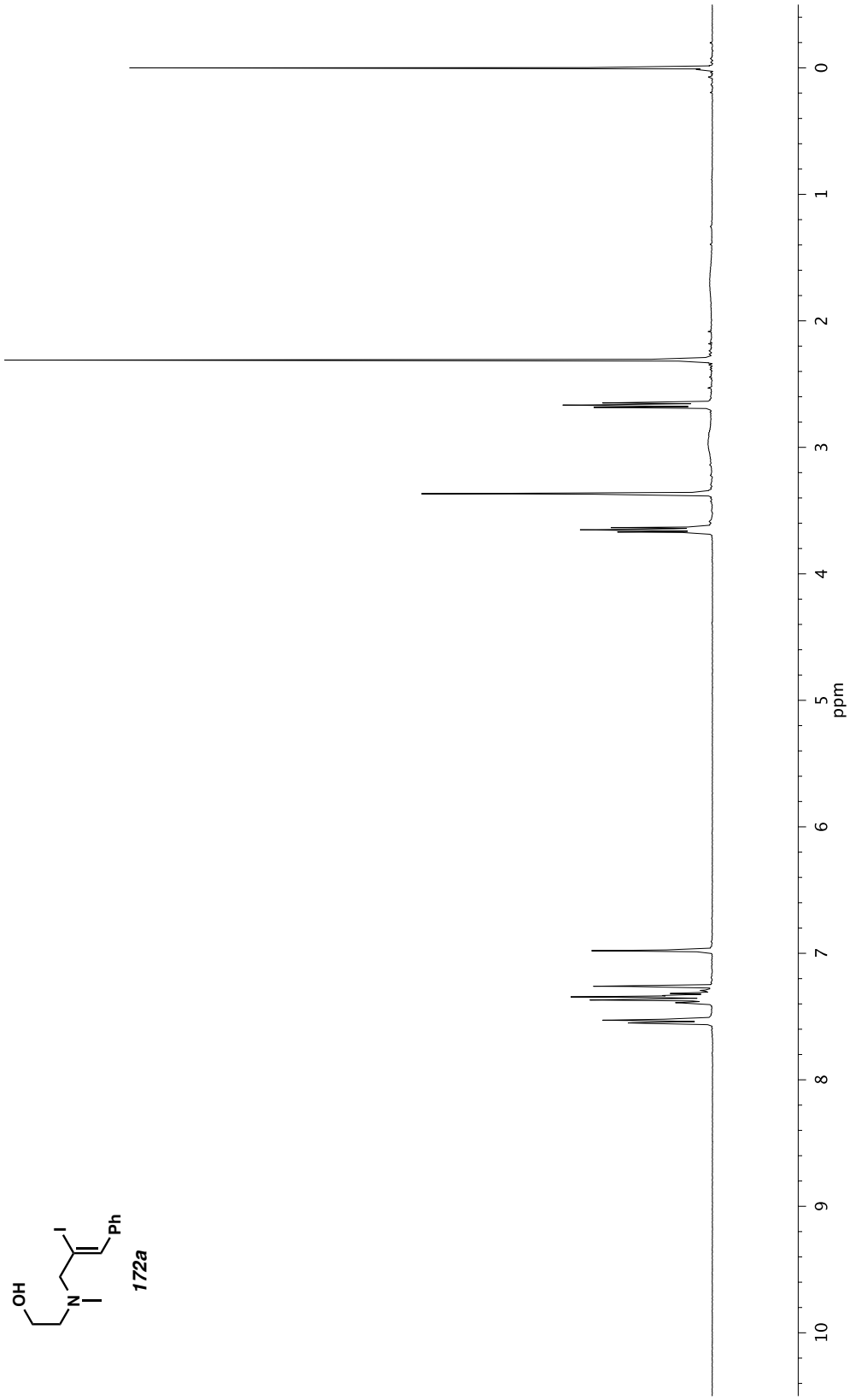


Figure A8.70. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **172a**.

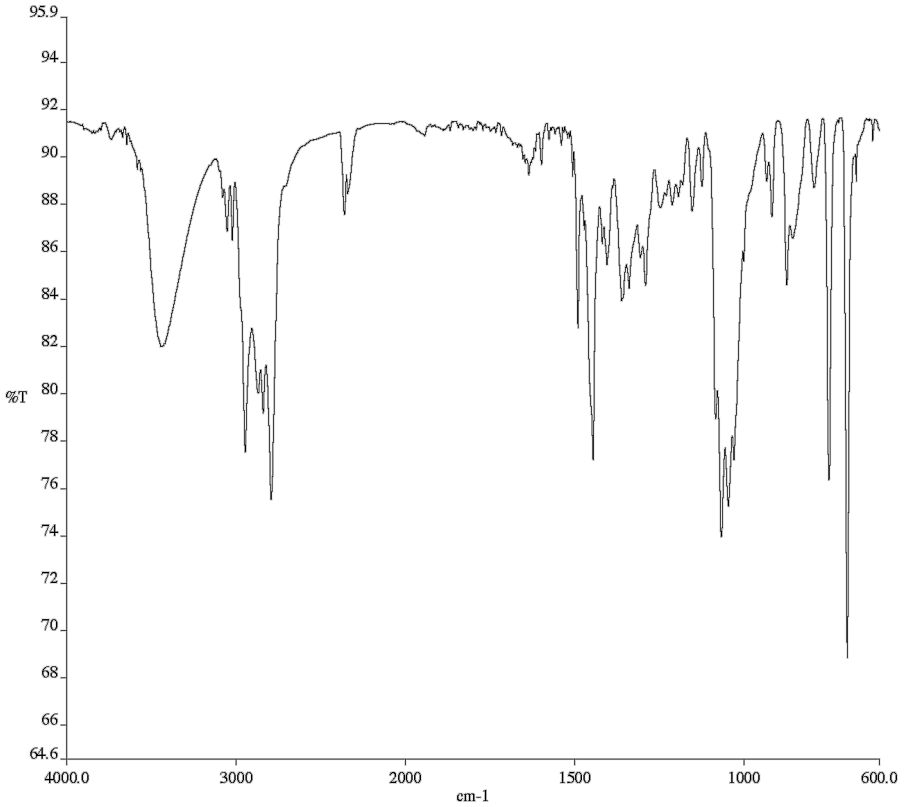


Figure A8.71. Infrared spectrum (Thin Film, NaCl) of compound **172a**.

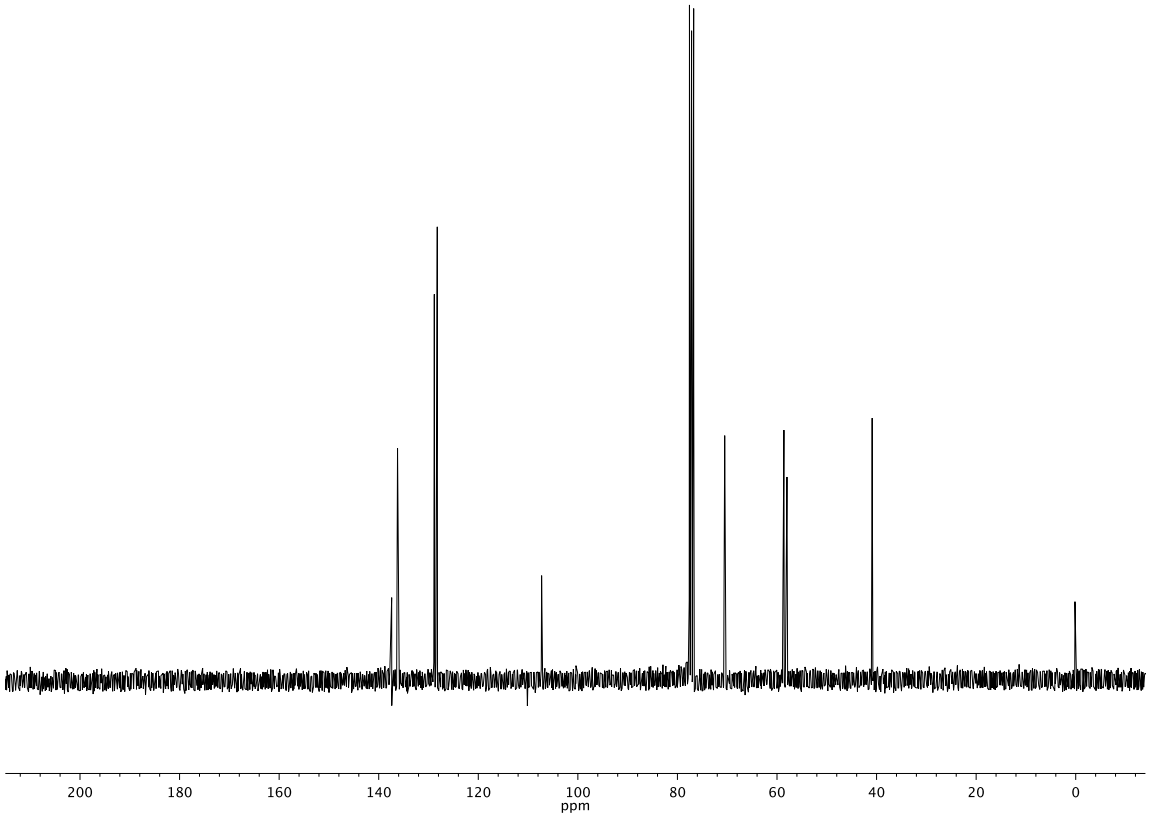


Figure A8.72. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **172a**.

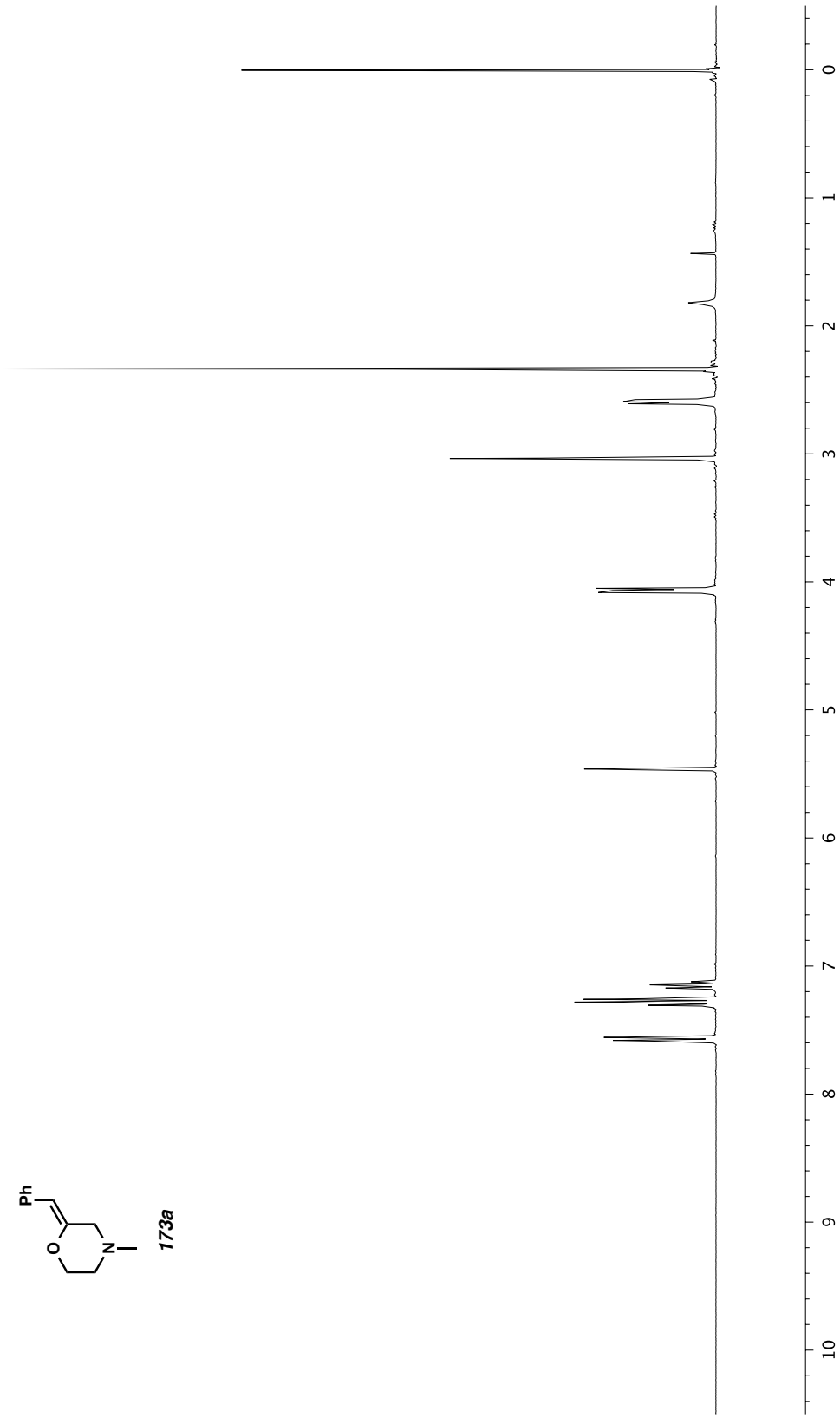


Figure A8.73. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **173a**.

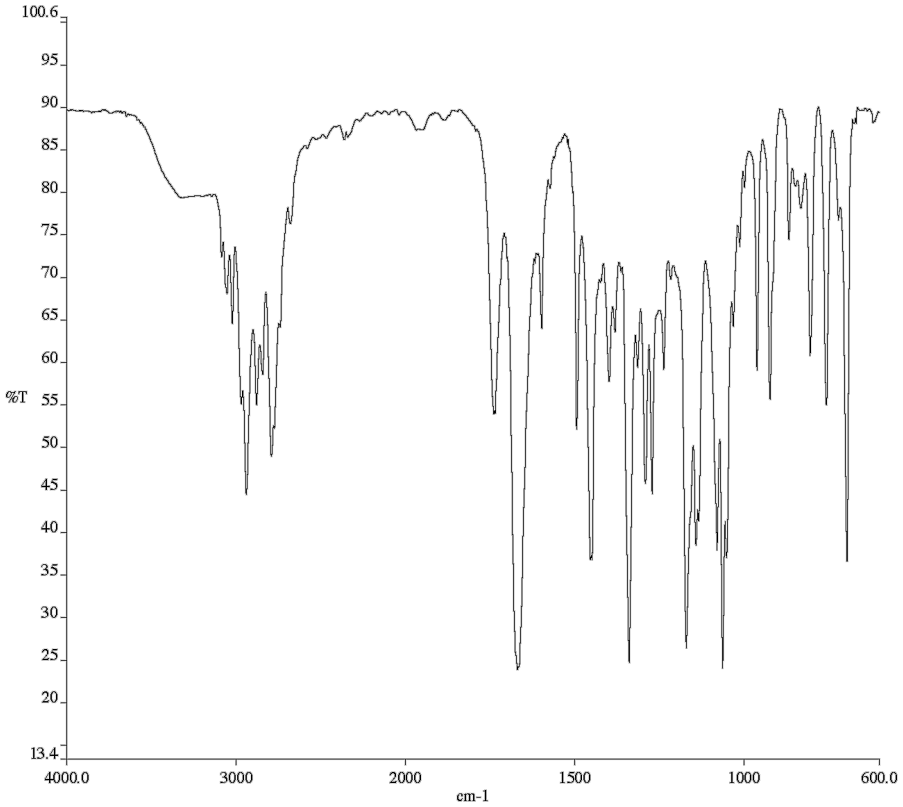


Figure A8.74. Infrared spectrum (Thin Film, NaCl) of compound **173a**.

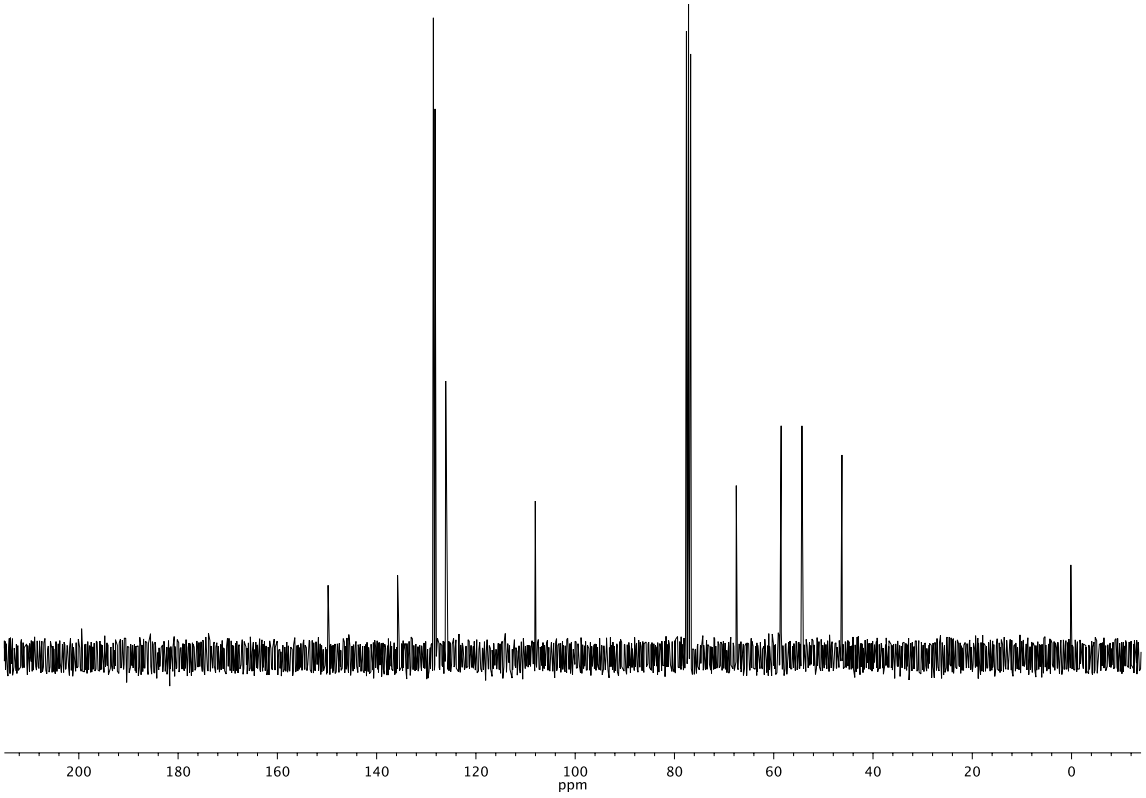


Figure A8.75. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **173a**.

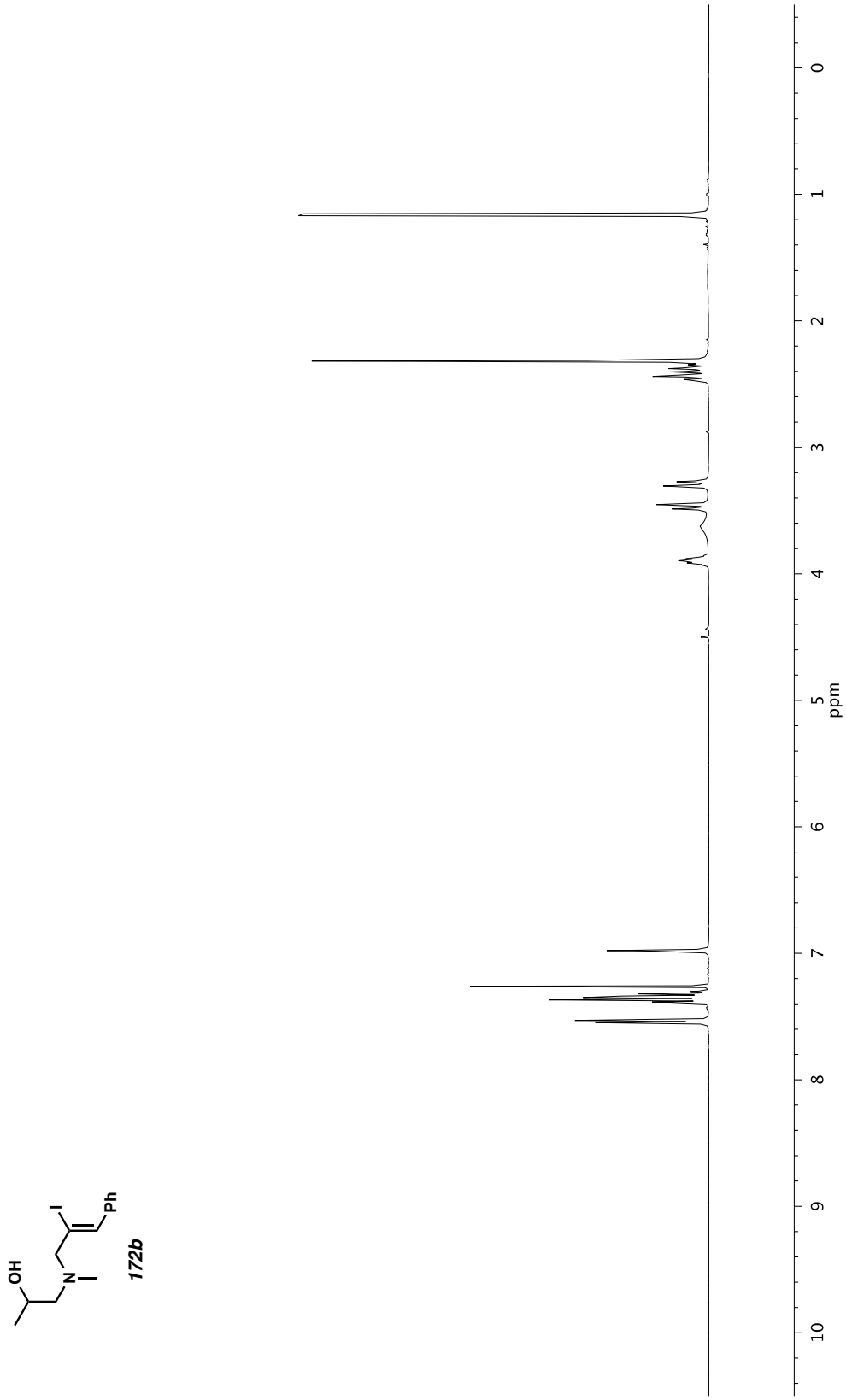


Figure A8.76. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **172b**.

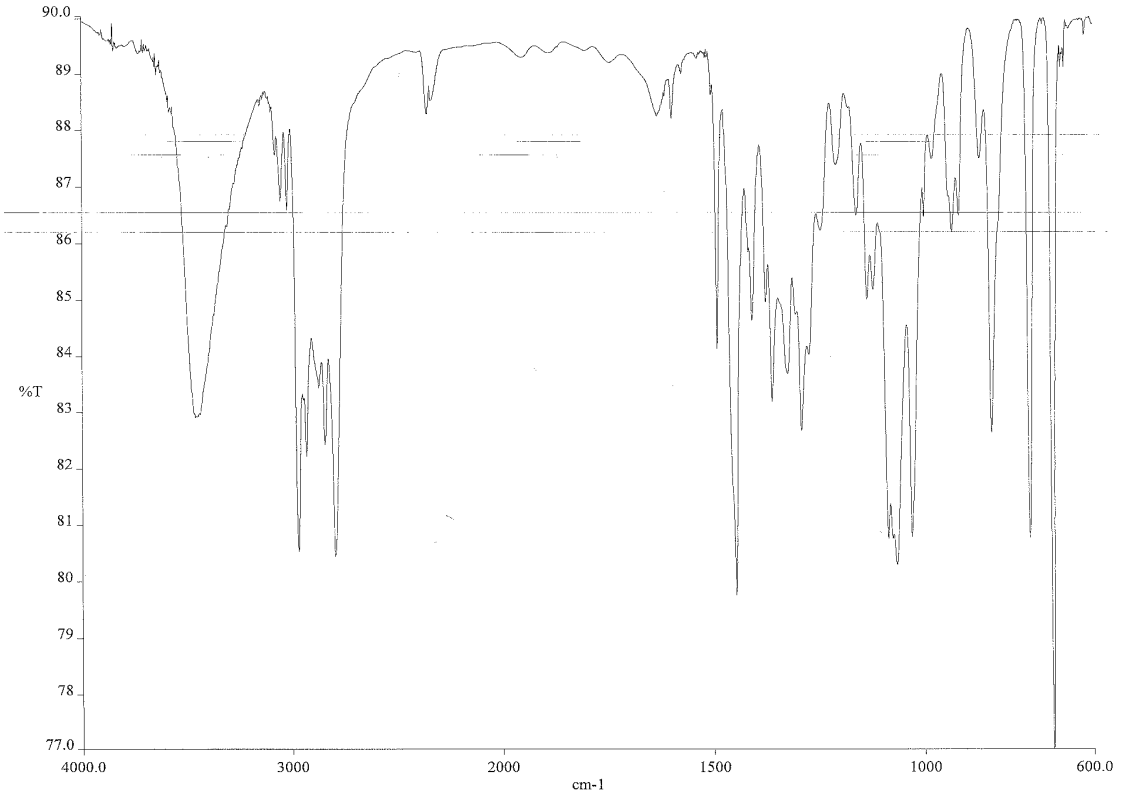


Figure A8.77. Infrared spectrum (Thin Film, NaCl) of compound **172b**.

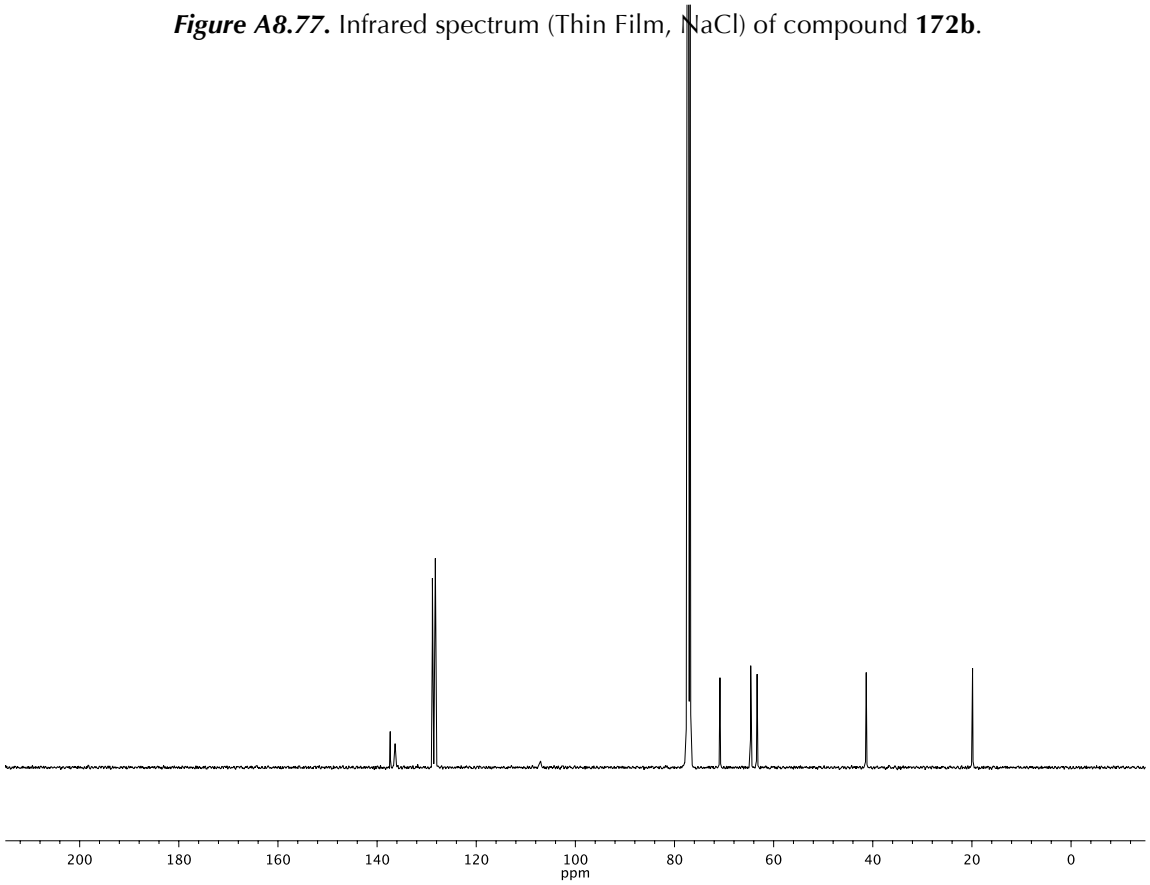


Figure A8.78. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **172b**.

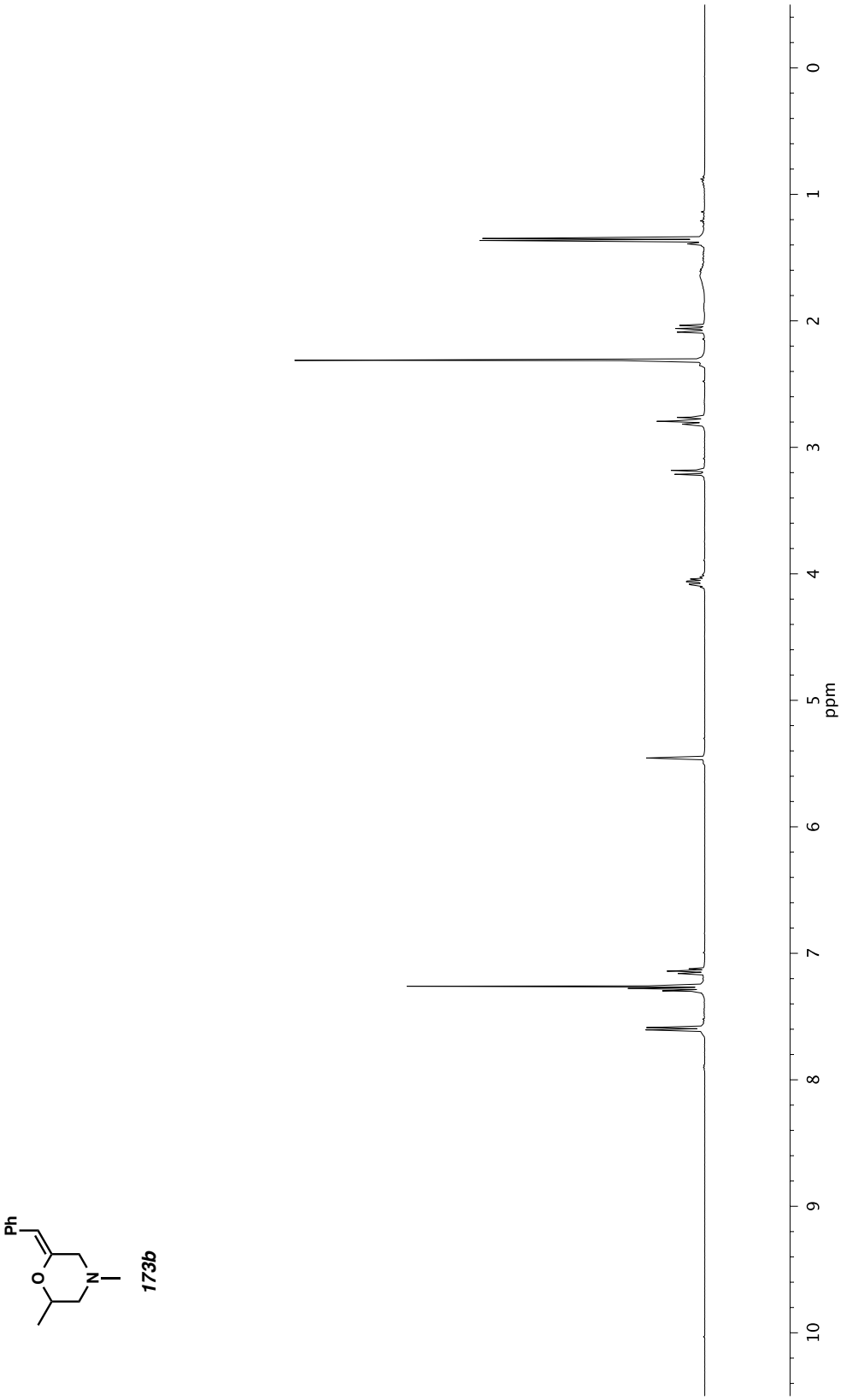


Figure A8.79. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **173b**.

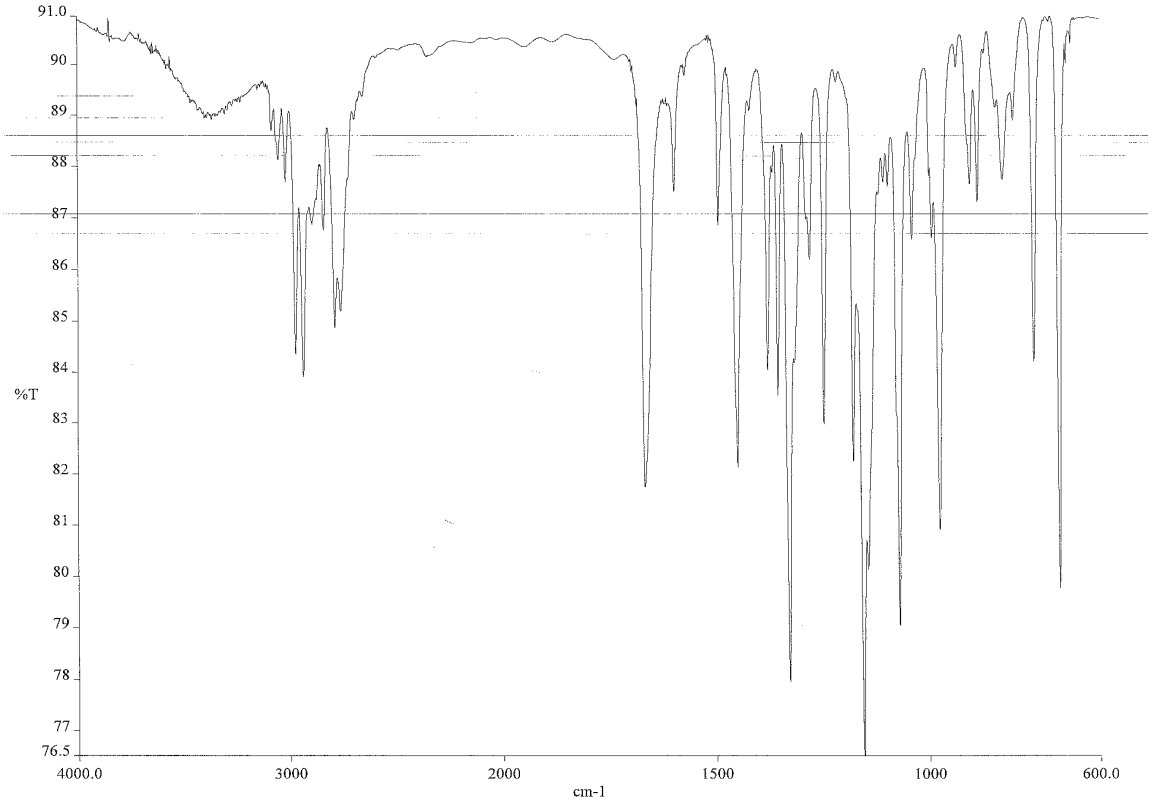


Figure A8.80. Infrared spectrum (Thin Film, NaCl) of compound **173b**.

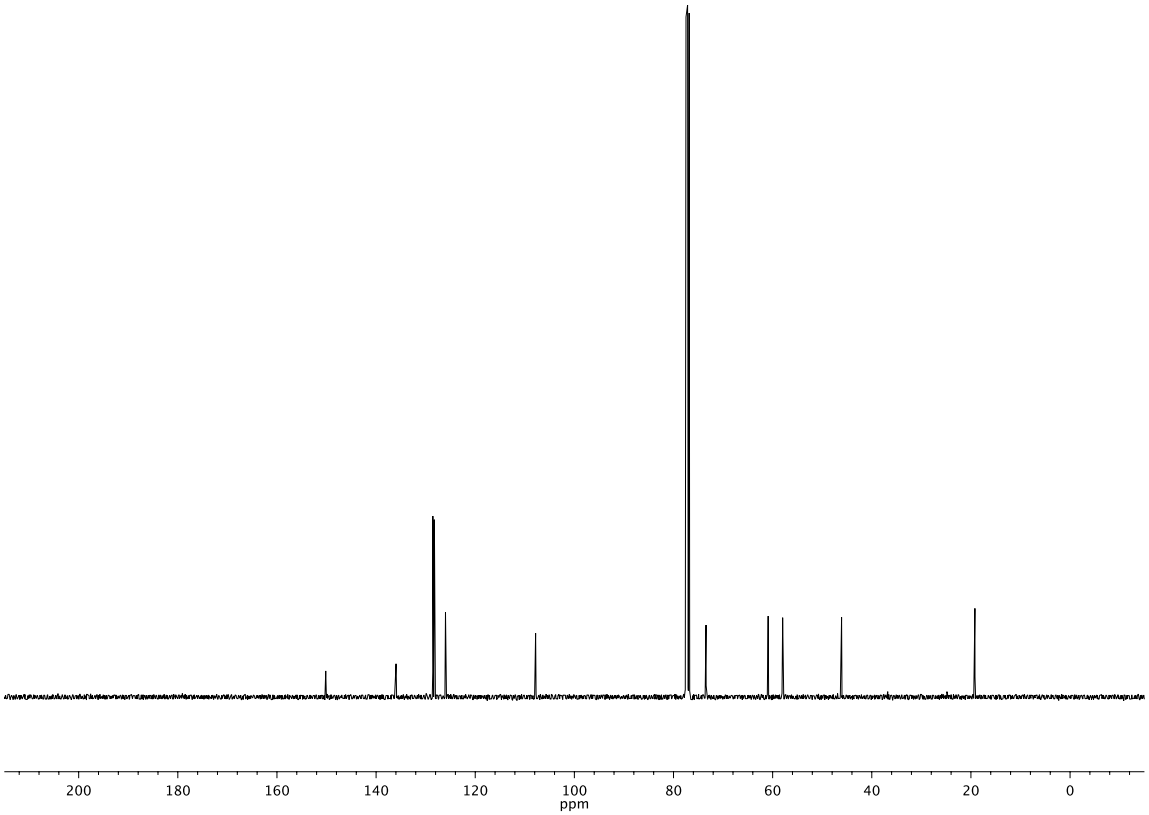


Figure A8.81. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **173b**.

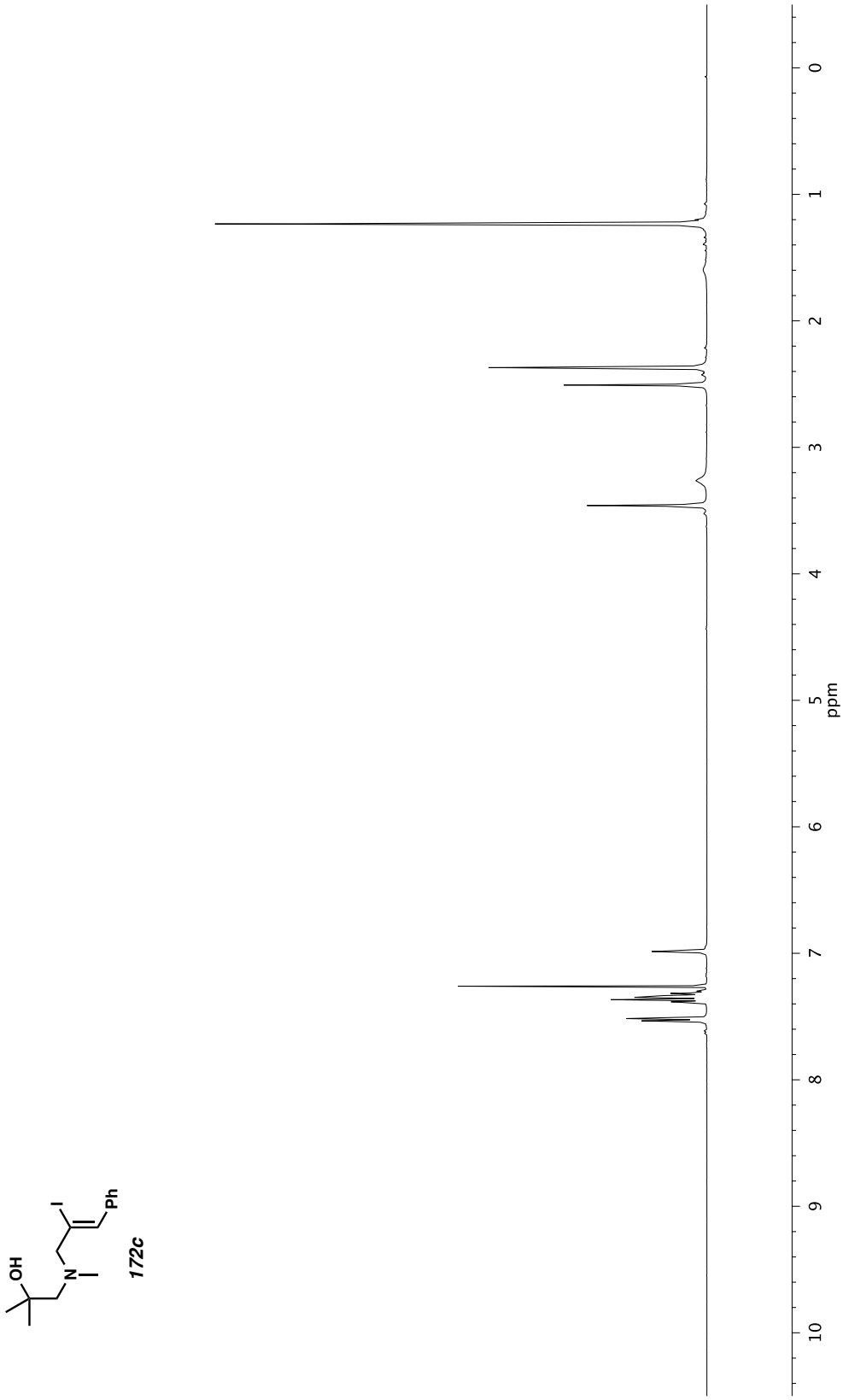


Figure A8.82. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **172c**.

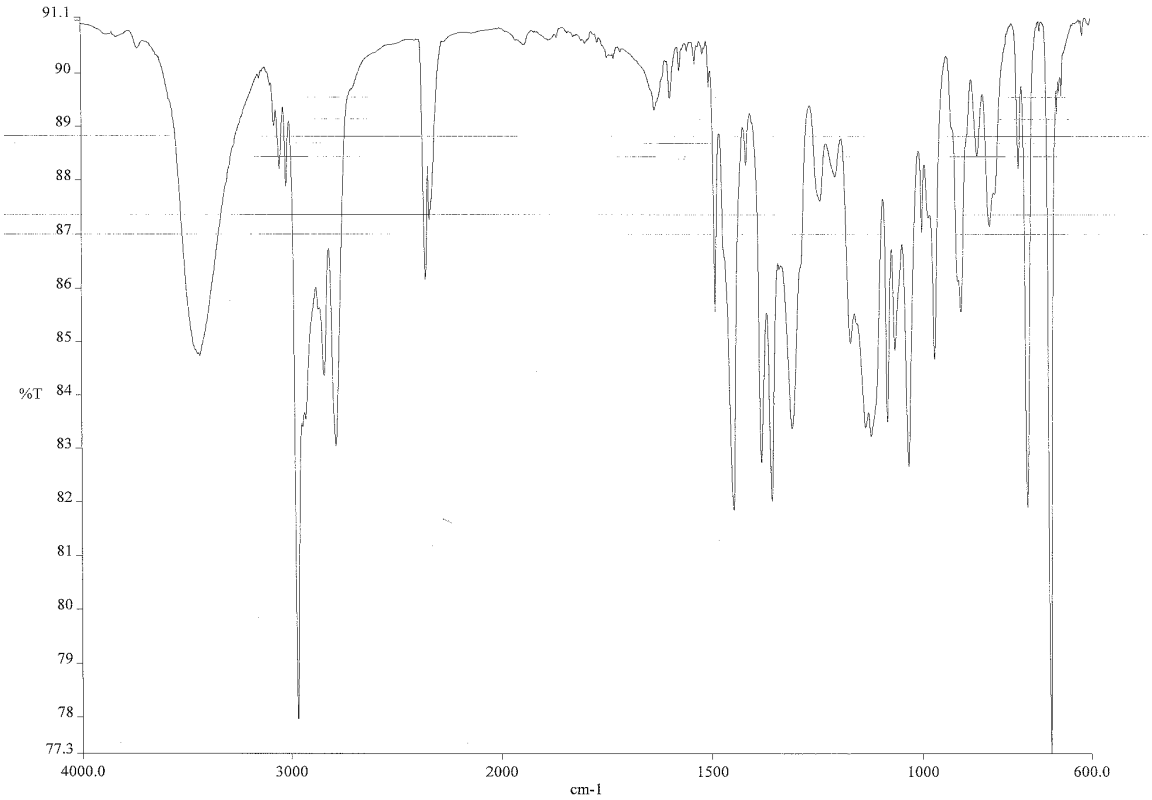


Figure A8.83. Infrared spectrum (Thin Film, NaCl) of compound **172c**.

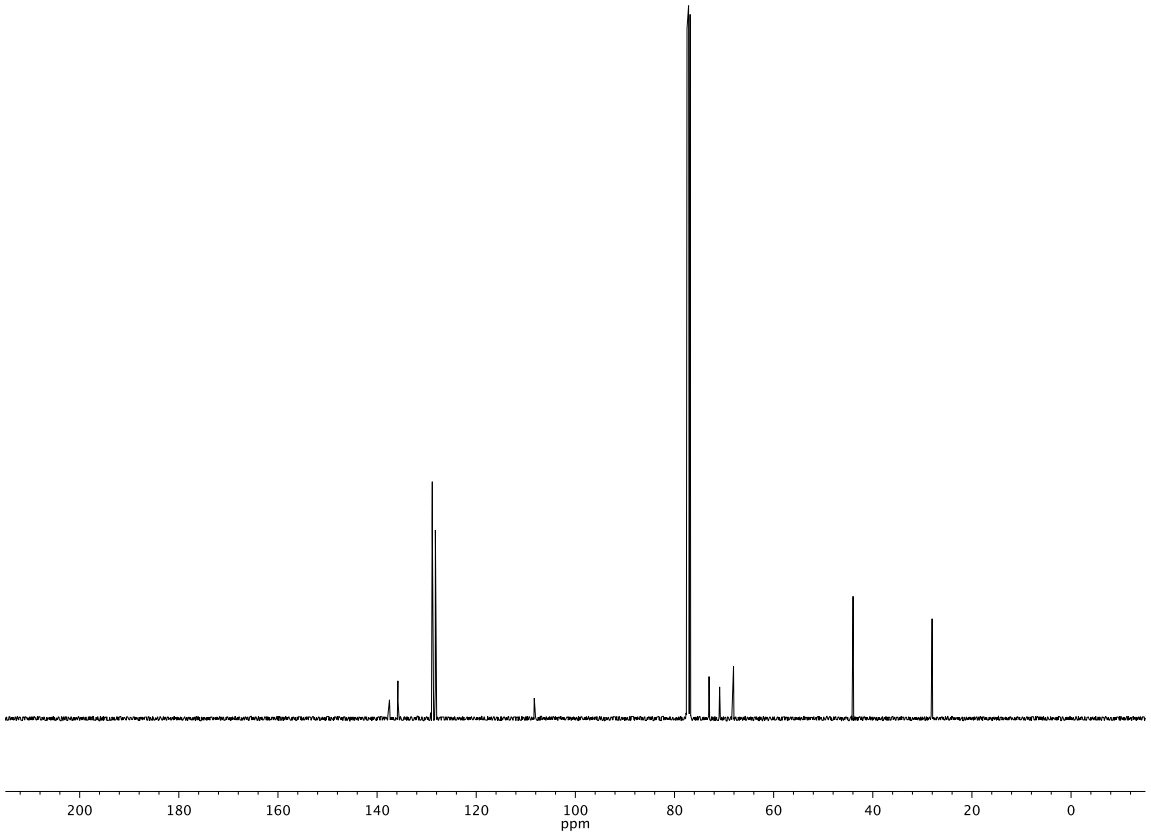


Figure A8.84. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **172c**.

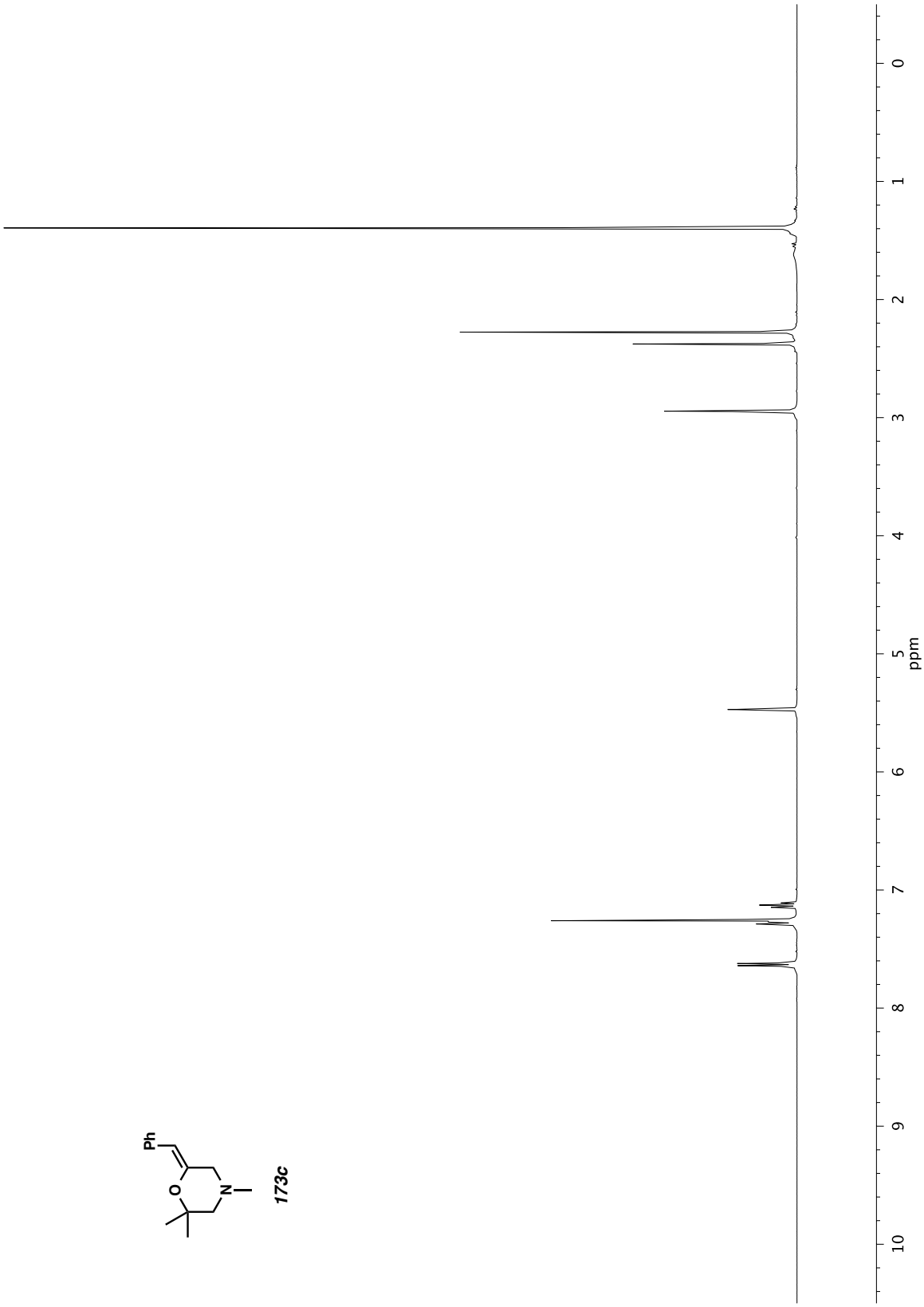


Figure A8.85. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **173c**.

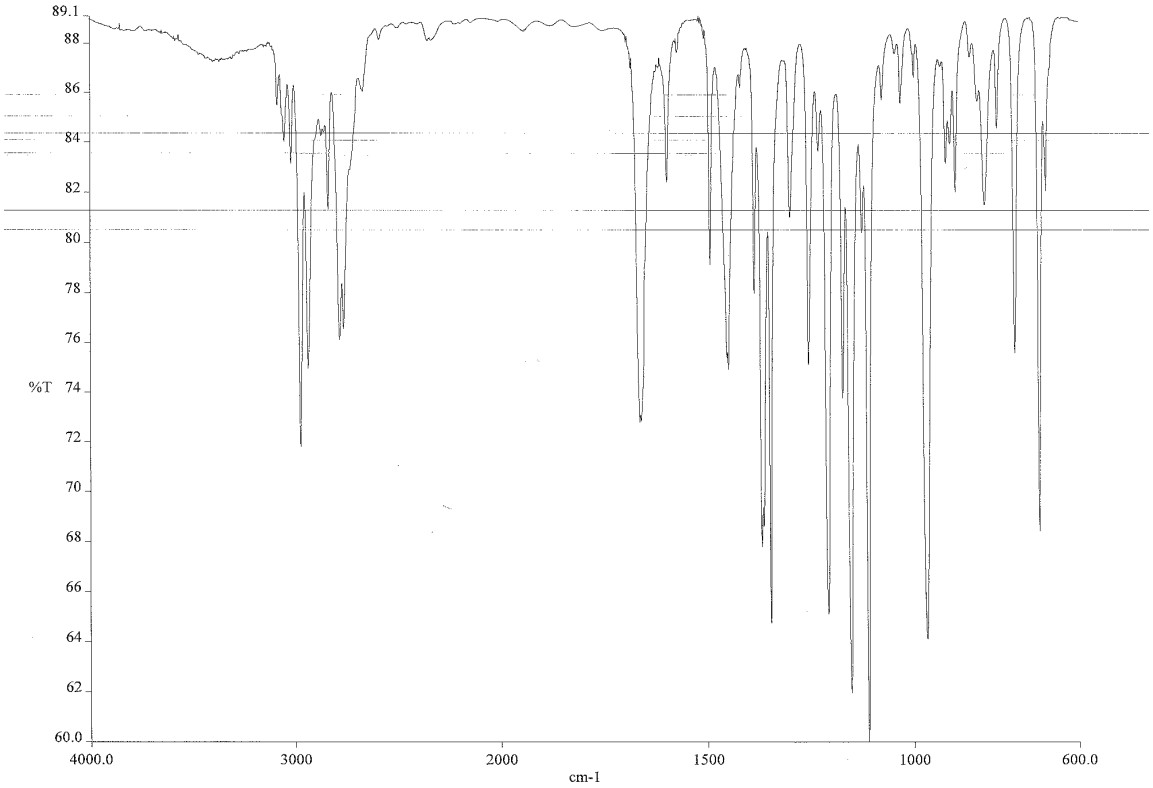


Figure A8.86. Infrared spectrum (Thin Film, NaCl) of compound **173c**.

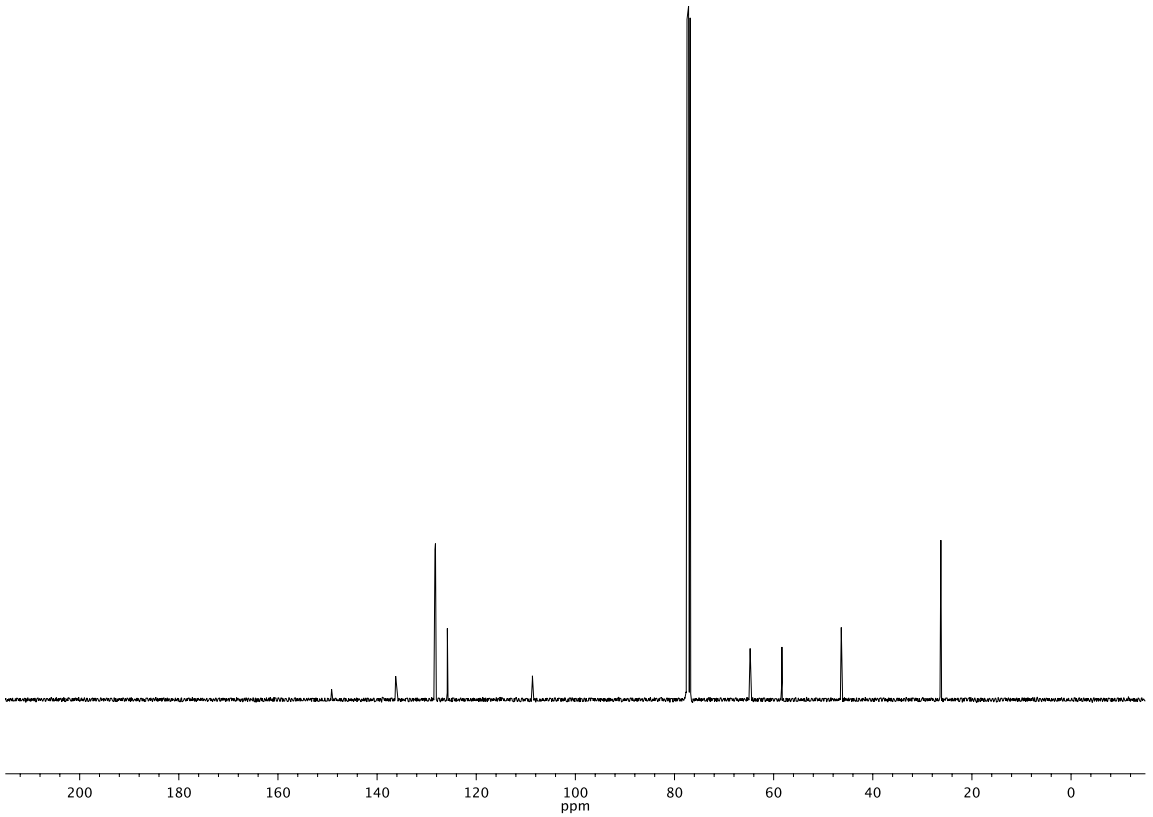


Figure A8.87. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **173c**.

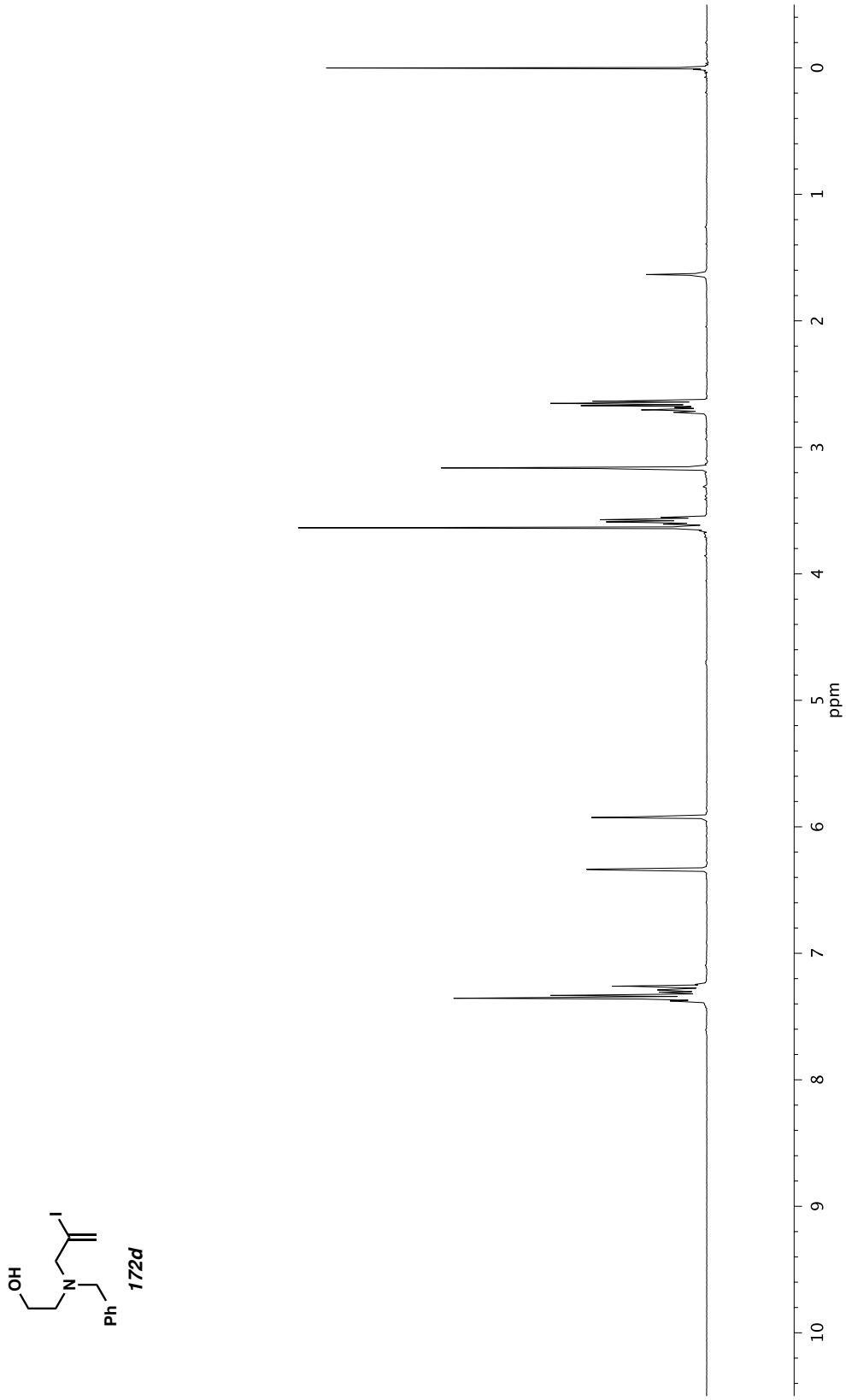


Figure A8.88. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **172d**.

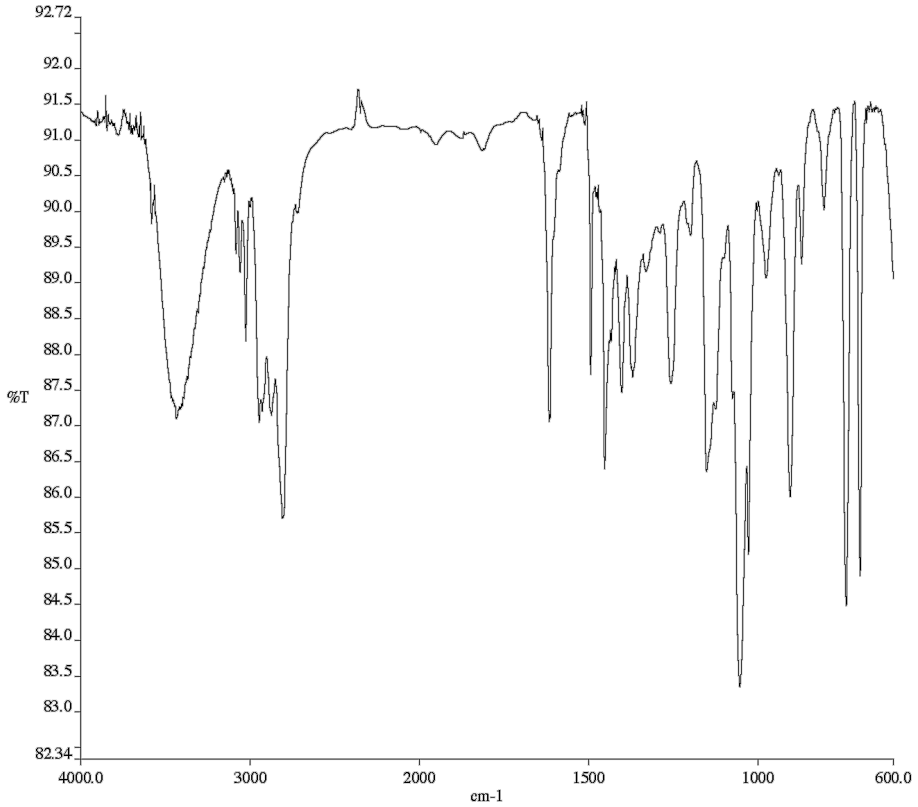


Figure A8.89. Infrared spectrum (Thin Film, NaCl) of compound **172d**.

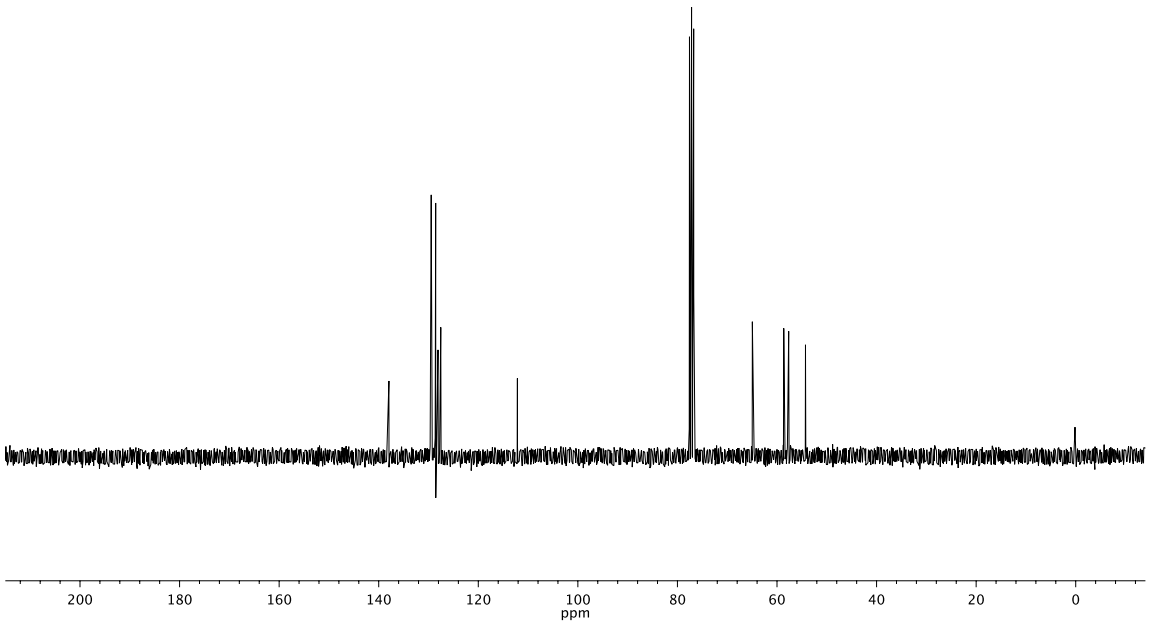


Figure A8.90. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **172d**.

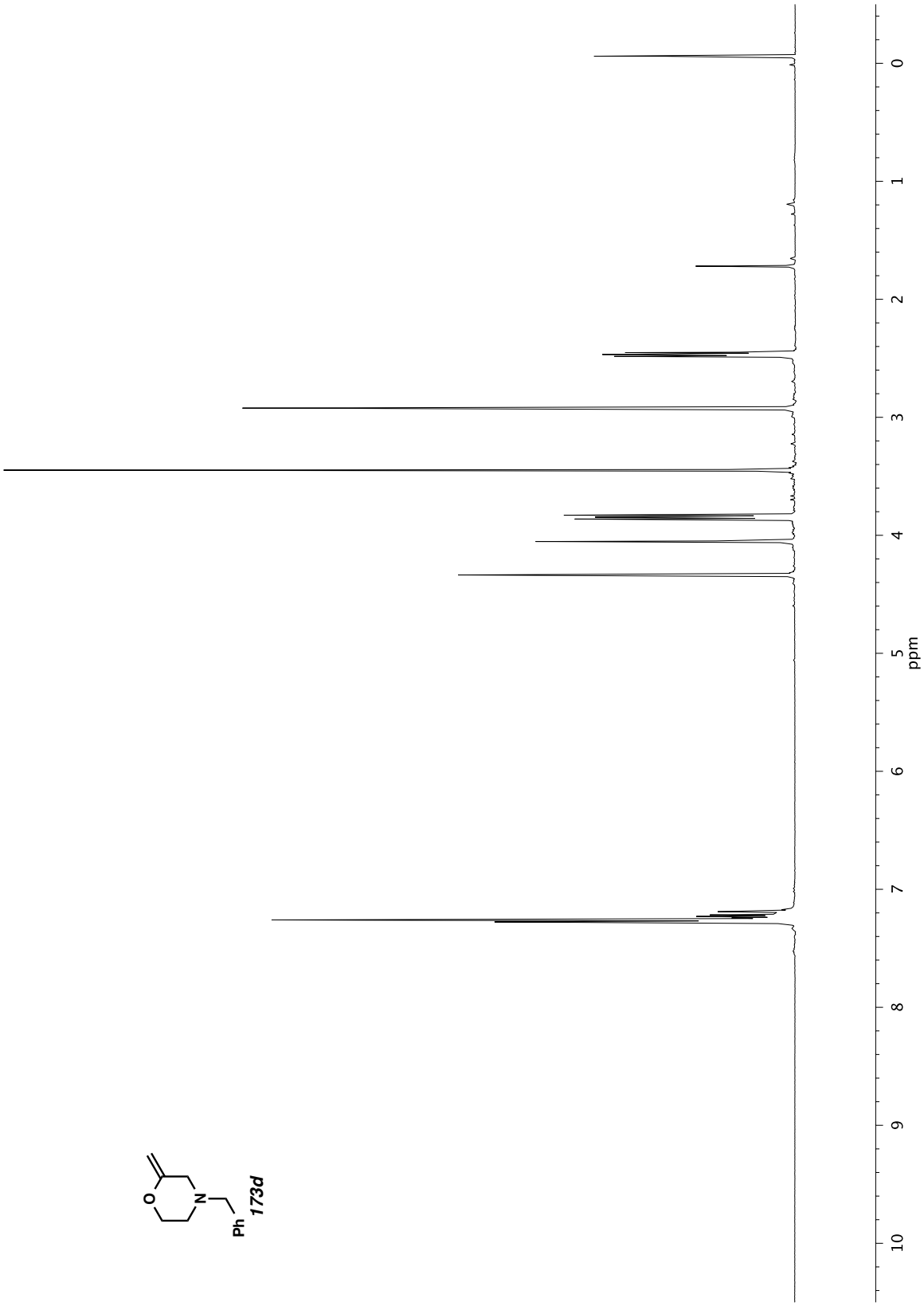


Figure A8.91. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **173d**.

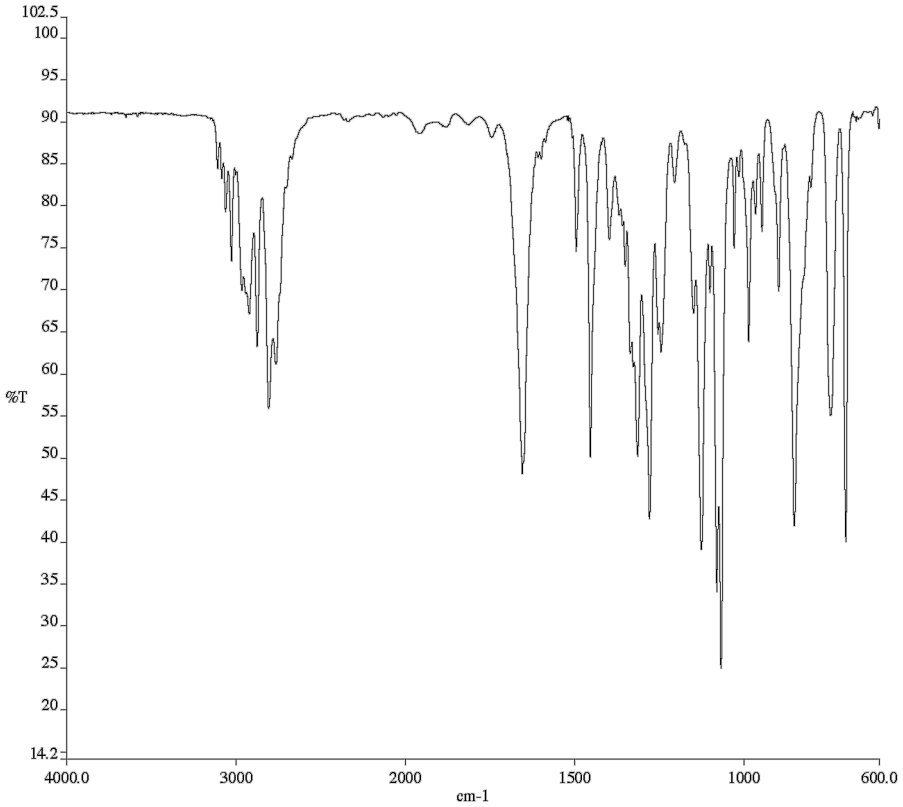


Figure A8.92. Infrared spectrum (Thin Film, NaCl) of compound **173d**.

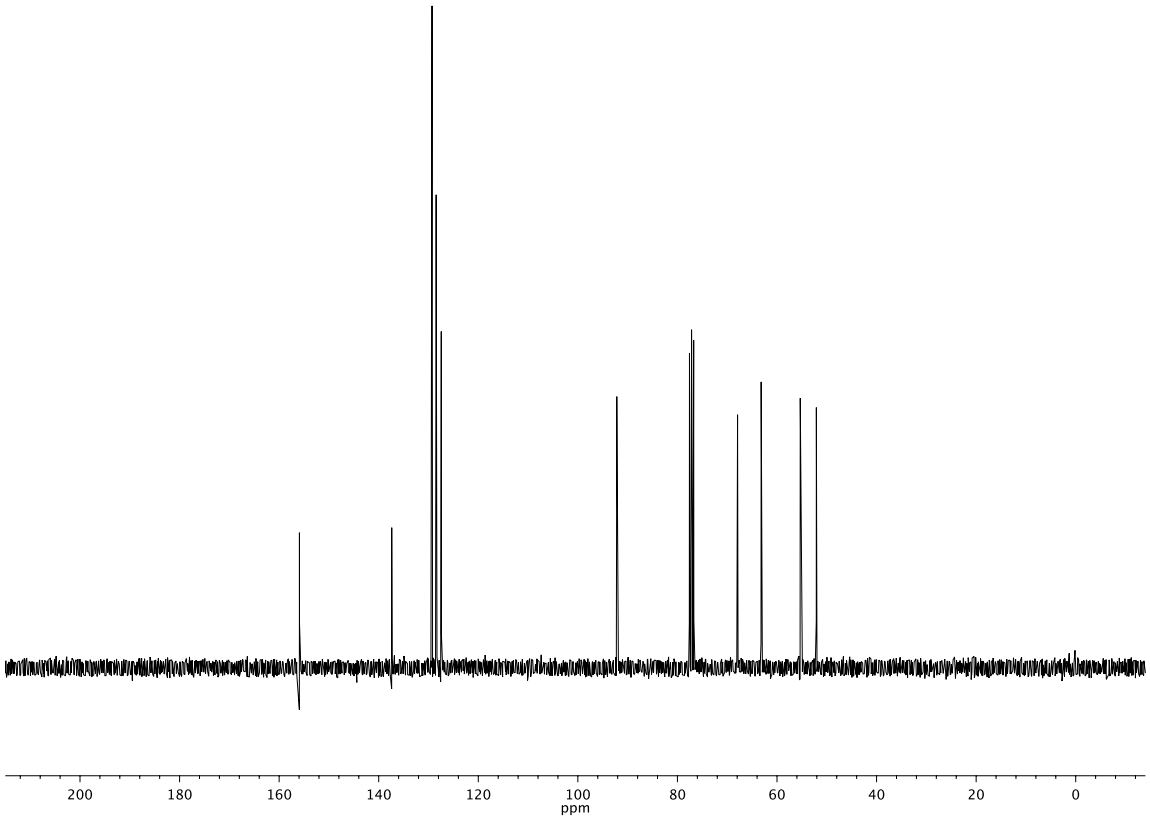


Figure A8.93. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **173d**.

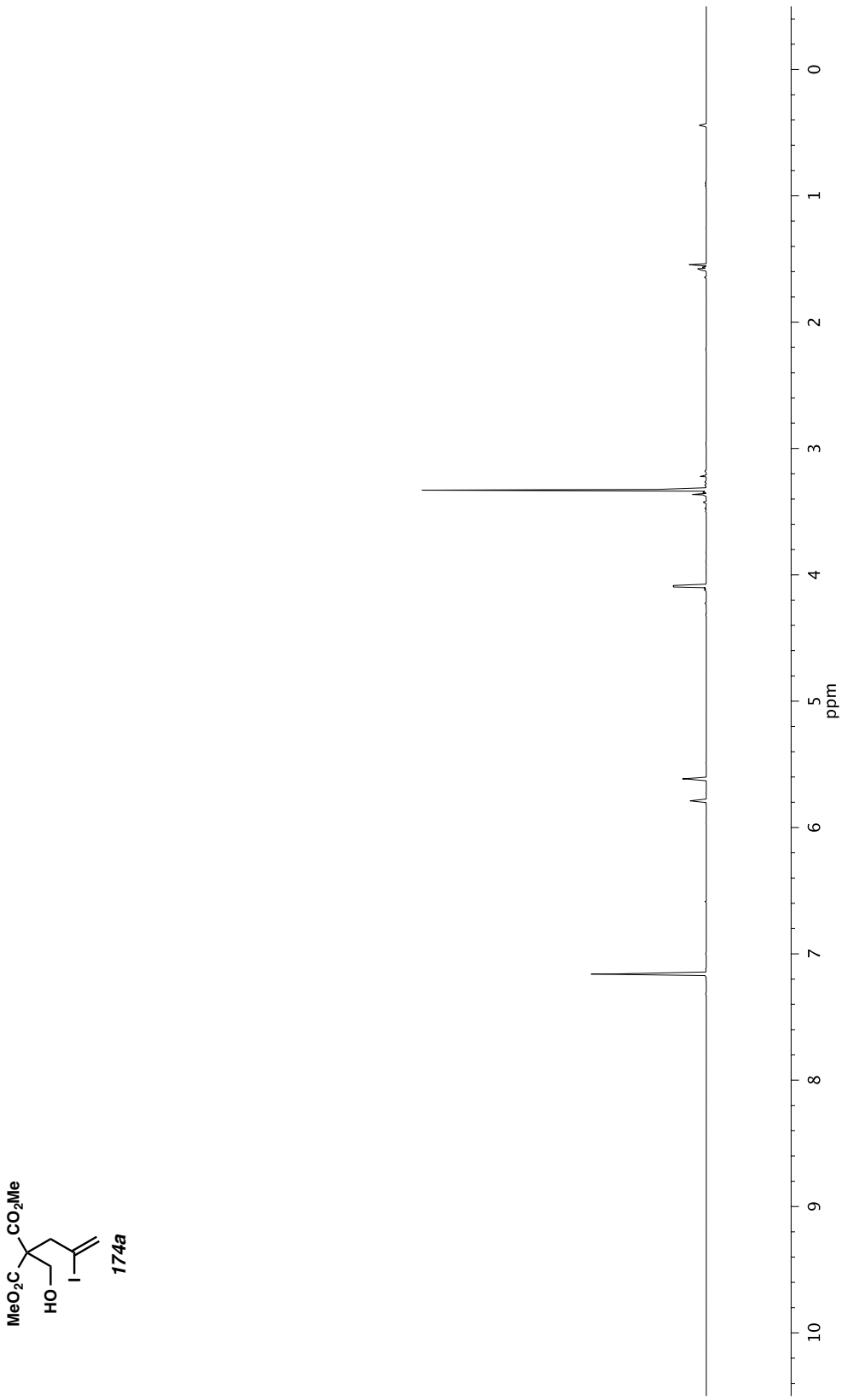


Figure A8.94. ^{1}H NMR (500 MHz, C_6D_6) of compound **174a**.

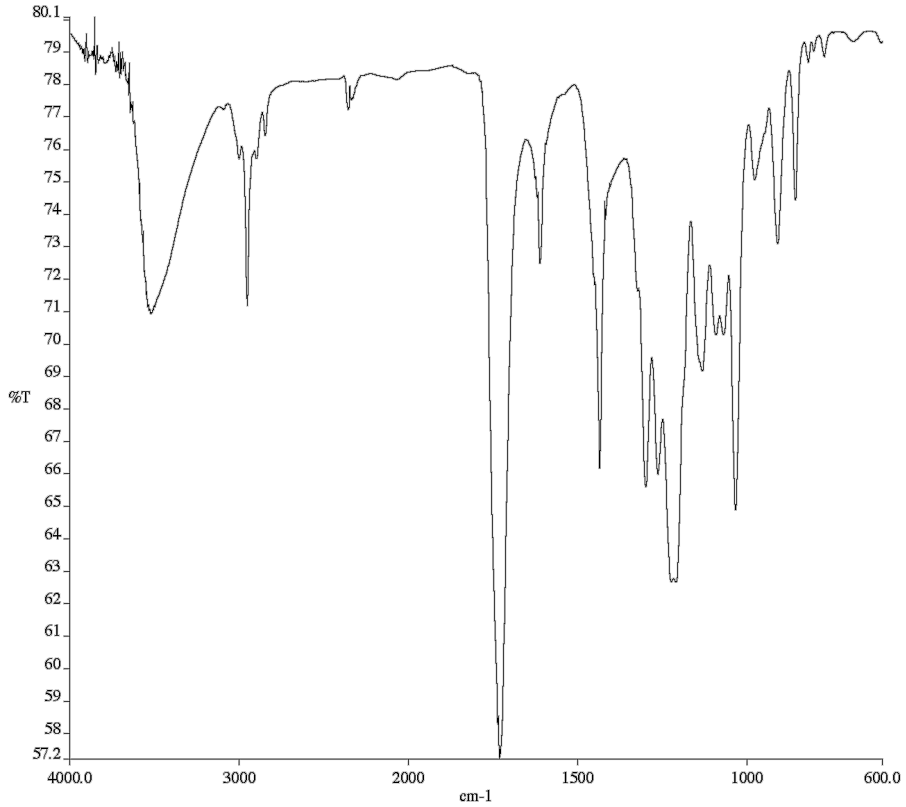


Figure A8.95. Infrared spectrum (Thin Film, NaCl) of compound **174a**.

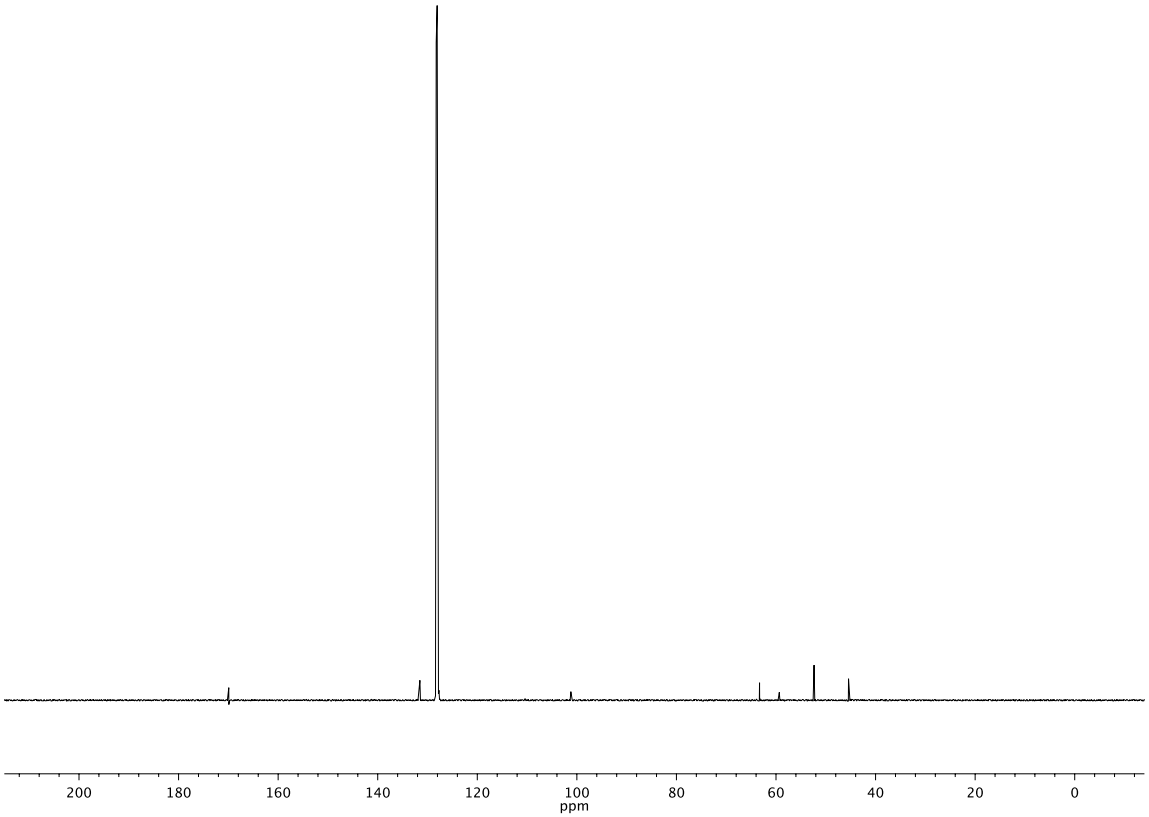


Figure A8.96. ^{13}C NMR (126 MHz, C_6D_6) of compound **174a**.

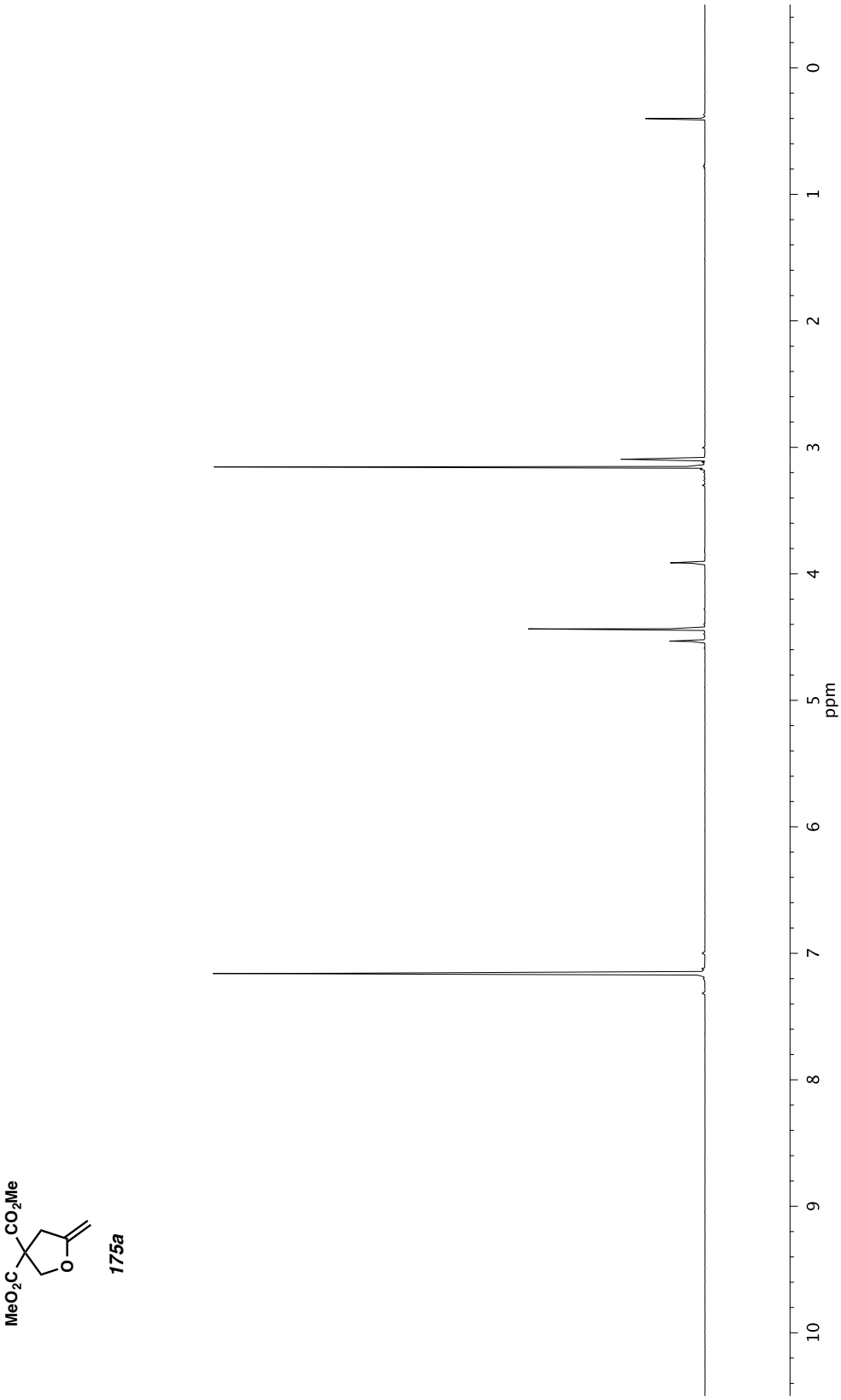


Figure A8.97. ^{1}H NMR (500 MHz, C_6D_6) of compound **175a**.

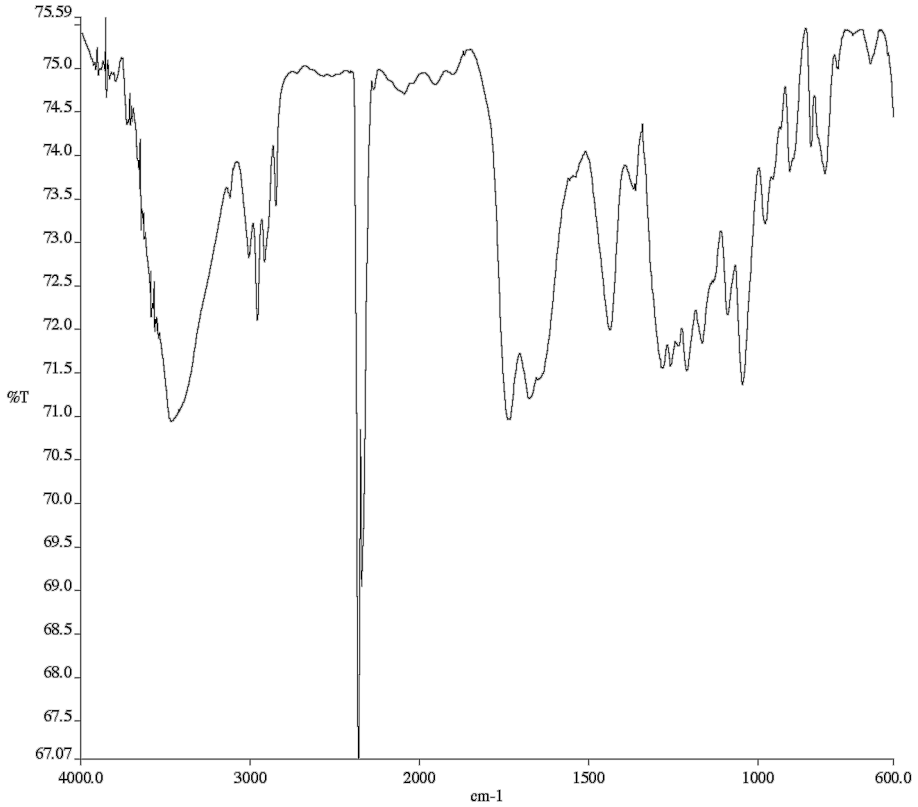


Figure A8.98. Infrared spectrum (Thin Film, NaCl) of compound **175a**.

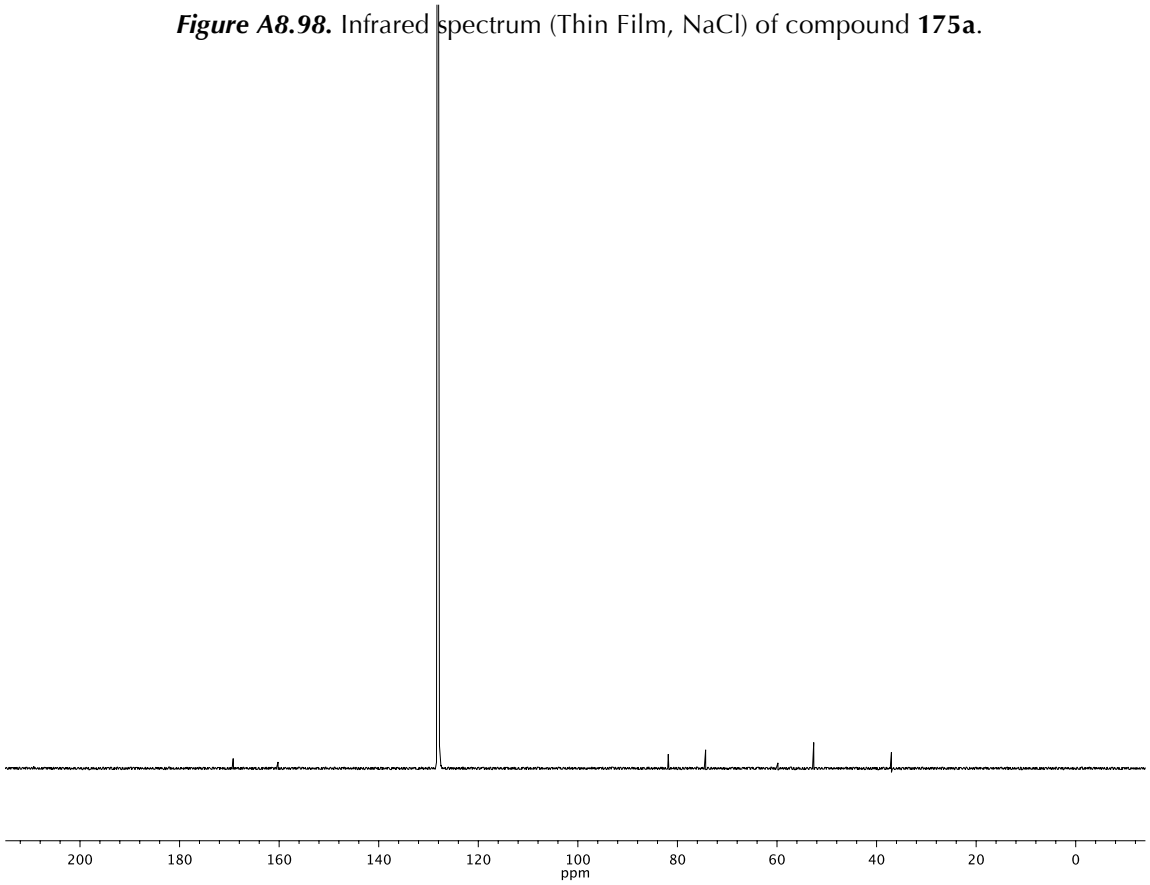


Figure A8.99. ^{13}C NMR (126 MHz, C_6D_6) of compound **175a**.

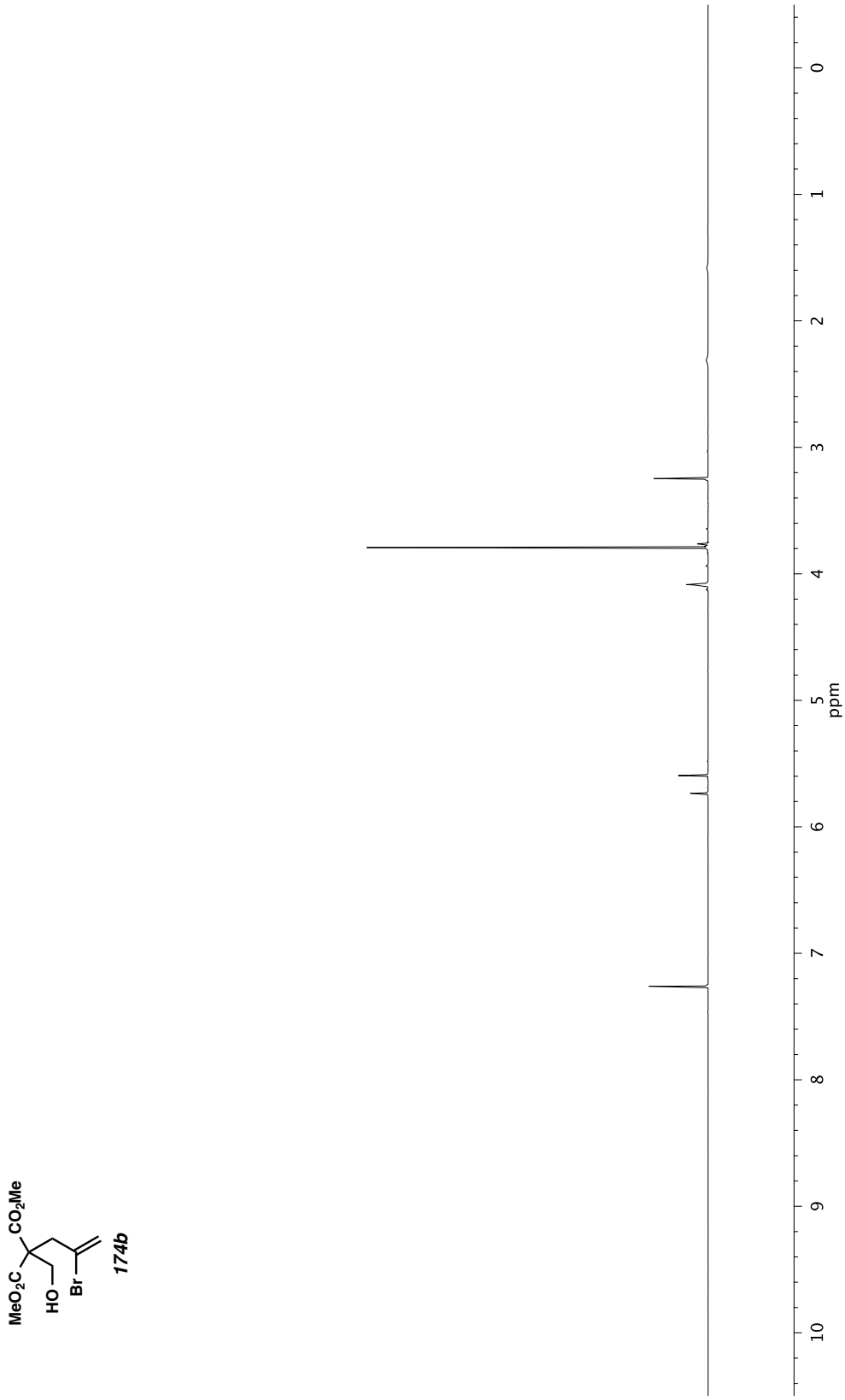


Figure A8.100. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **174b**.

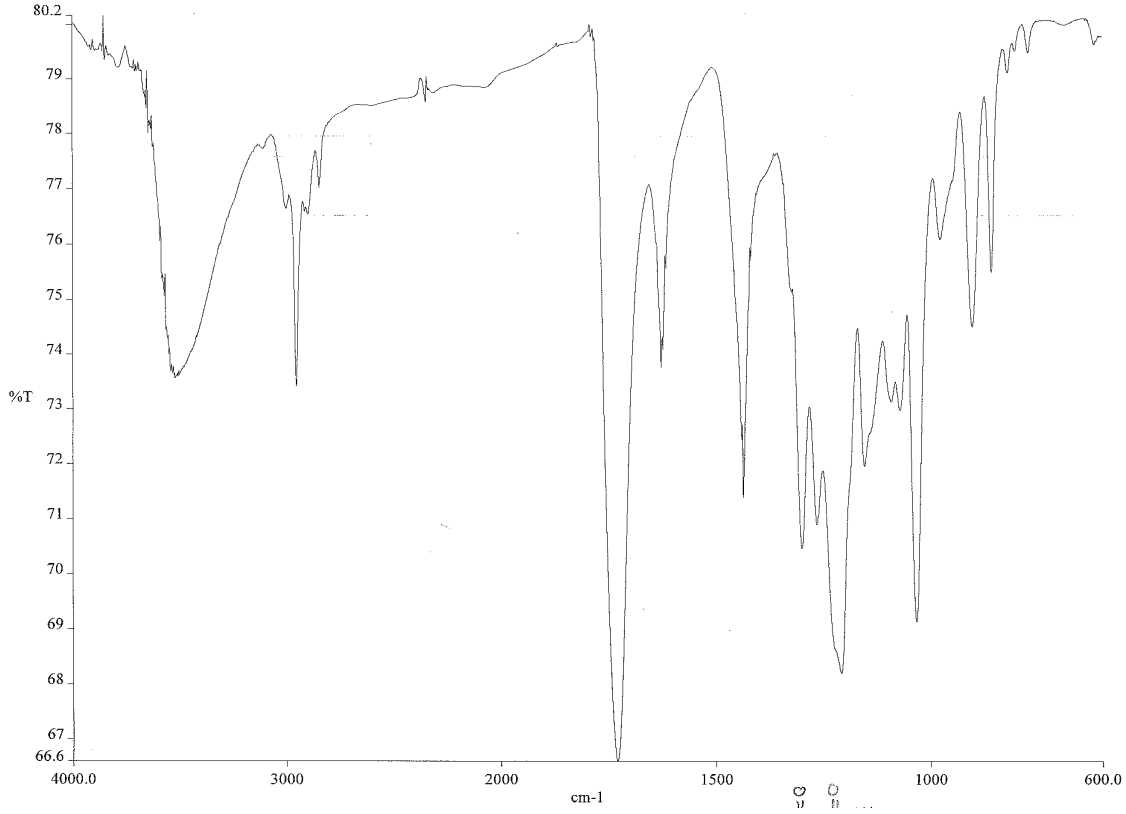


Figure A8.101. Infrared spectrum (Thin Film, NaCl) of compound **174b**.

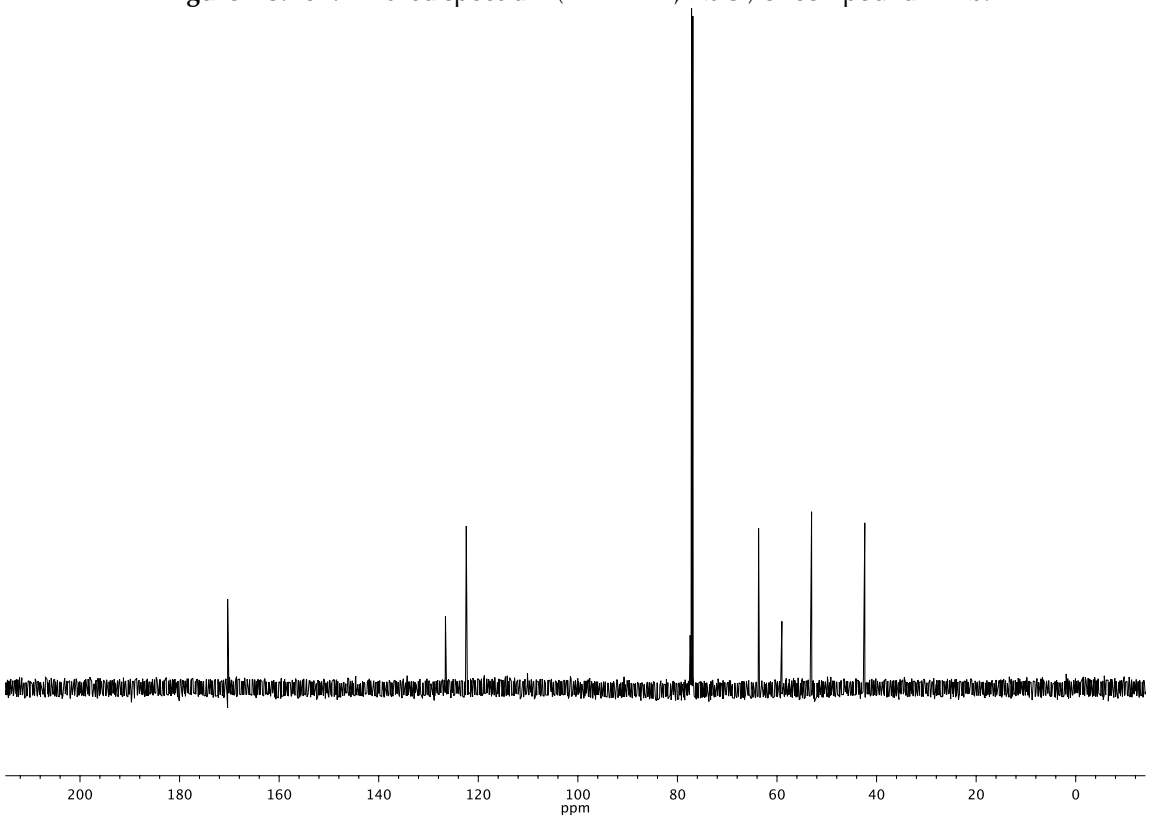


Figure A8.102. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **174b**.

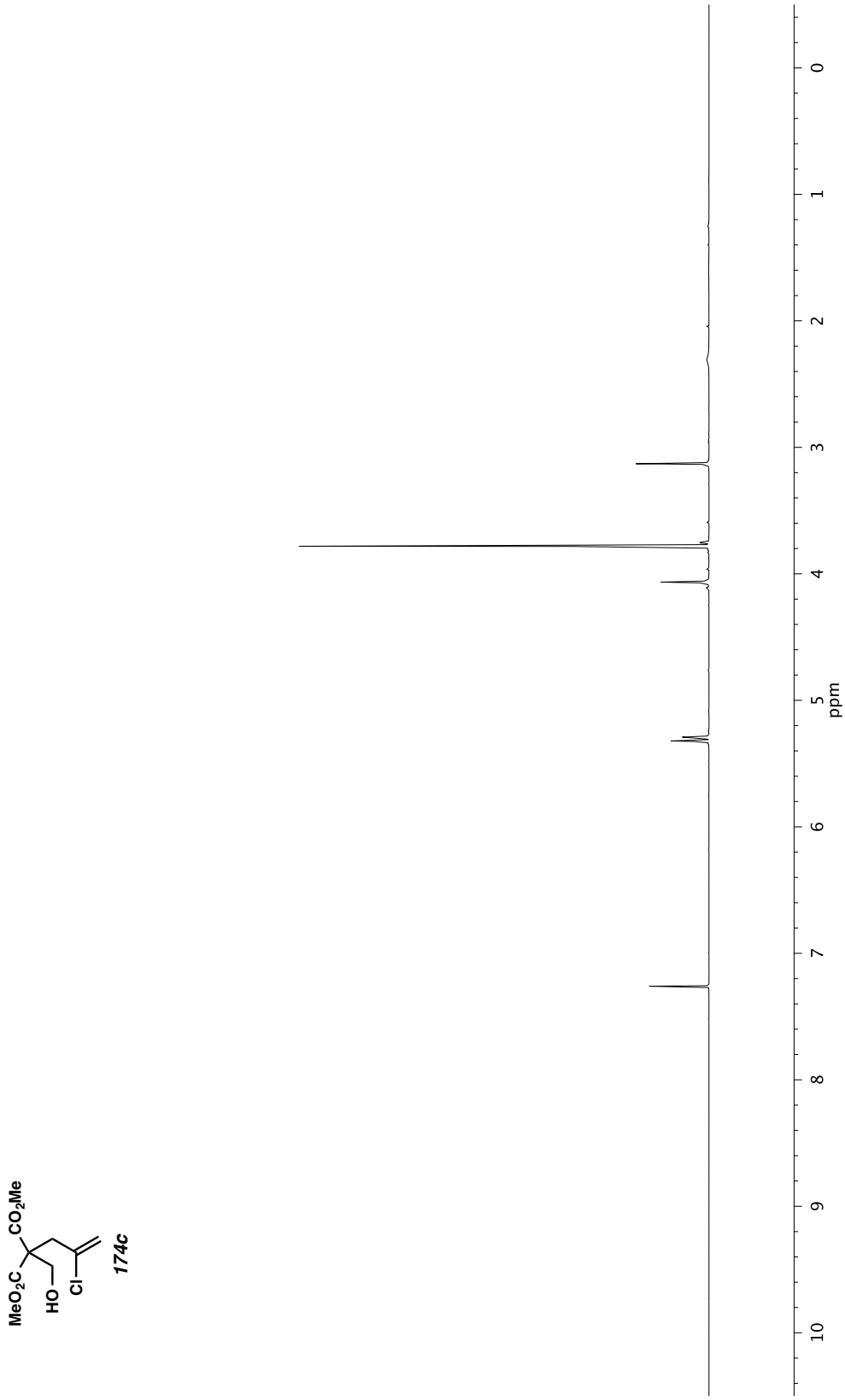


Figure A8.103. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **174c**.

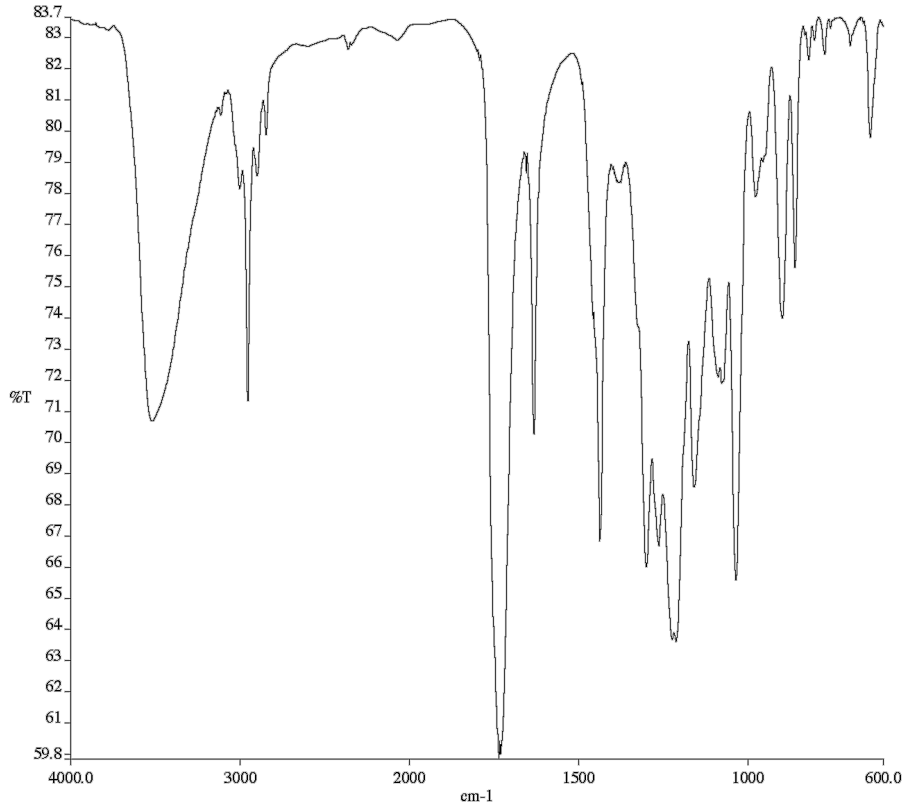


Figure A8.104. Infrared spectrum (Thin Film, NaCl) of compound **174c**.

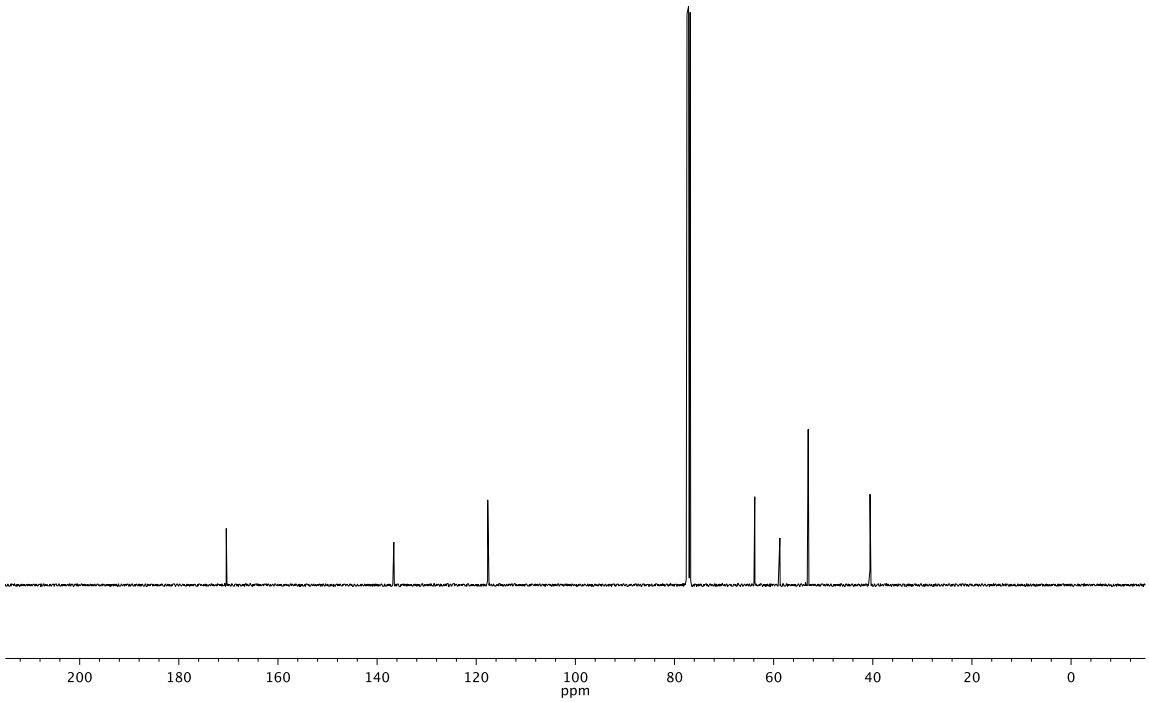


Figure A8.105. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **174c**.

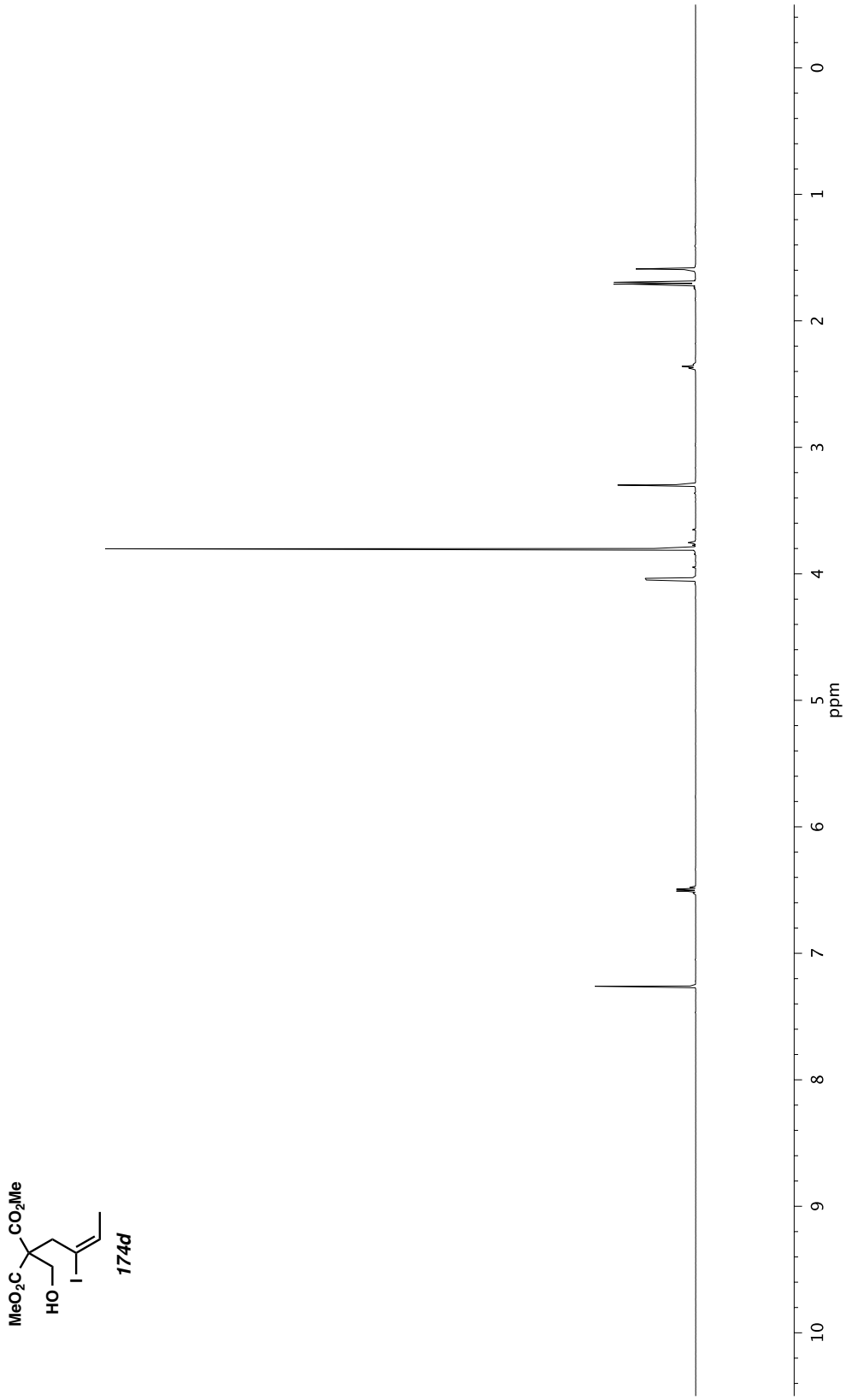


Figure A8.106. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **174d**.

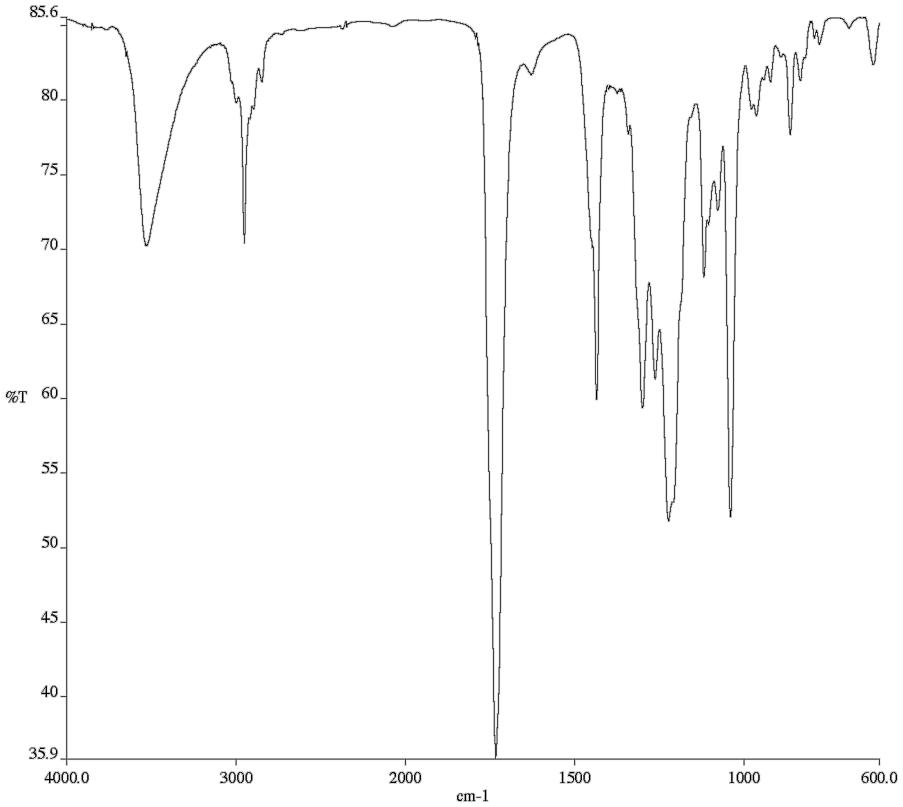


Figure A8.107. Infrared spectrum (Thin Film, NaCl) of compound **174d**.

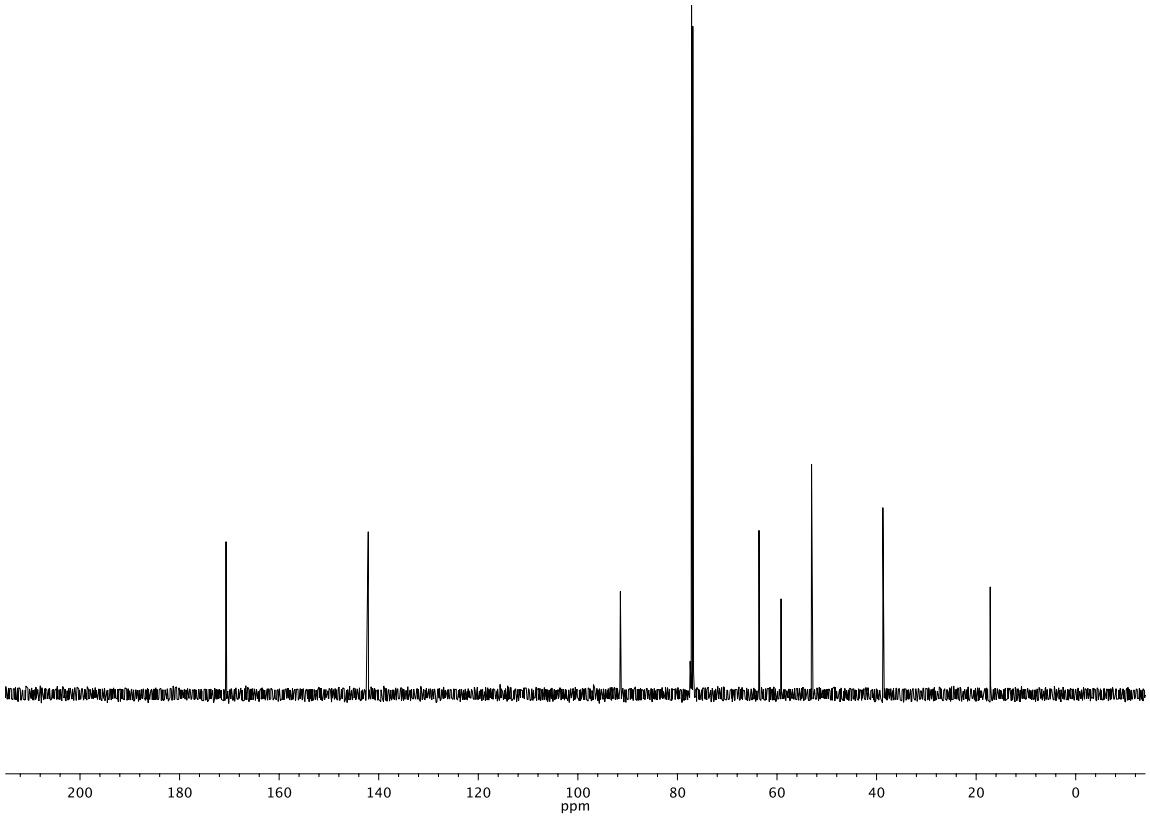


Figure A8.108. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **174d**.

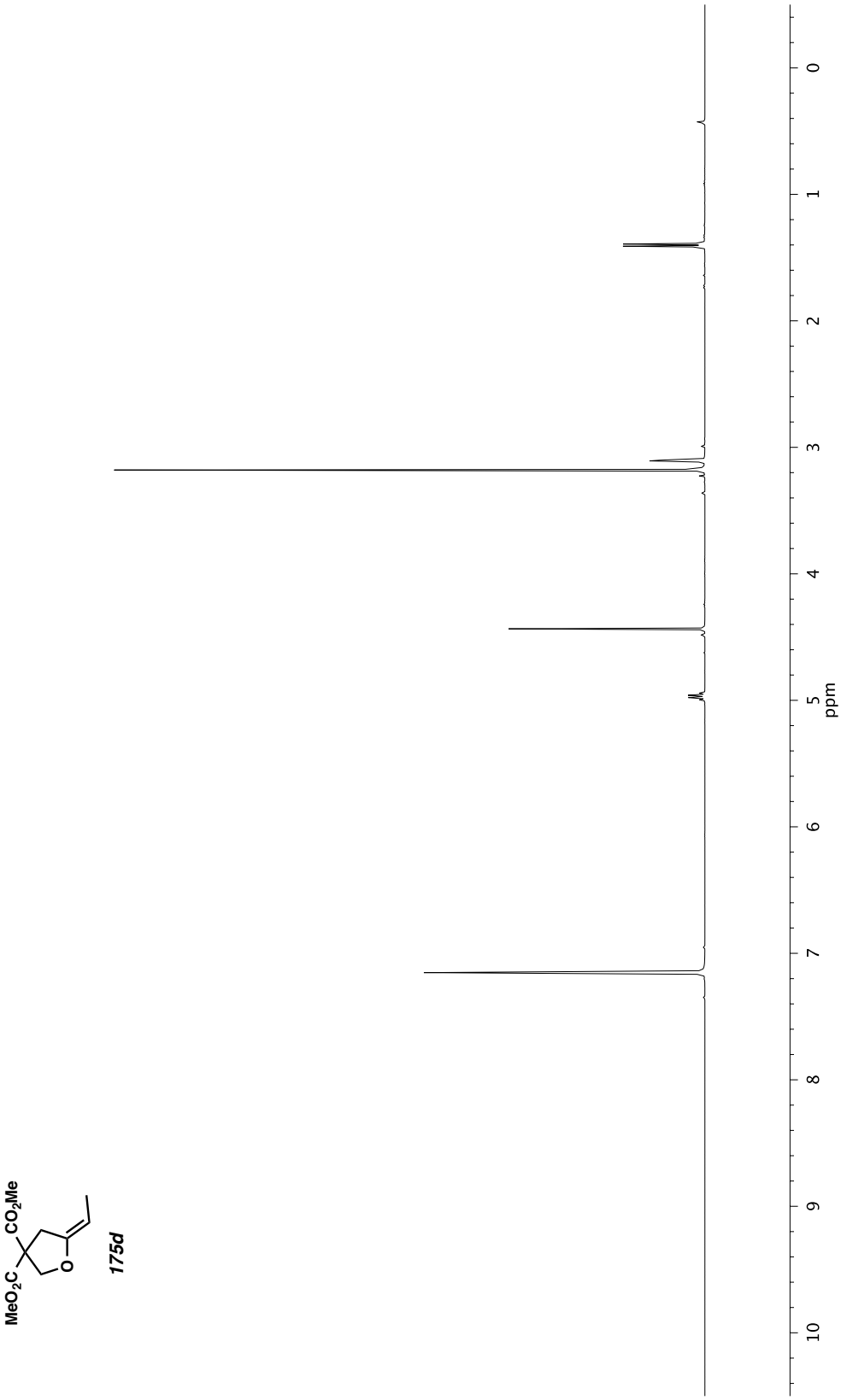


Figure A8.109. ^{1}H NMR (400 MHz, C_6D_6) of compound **175d**.

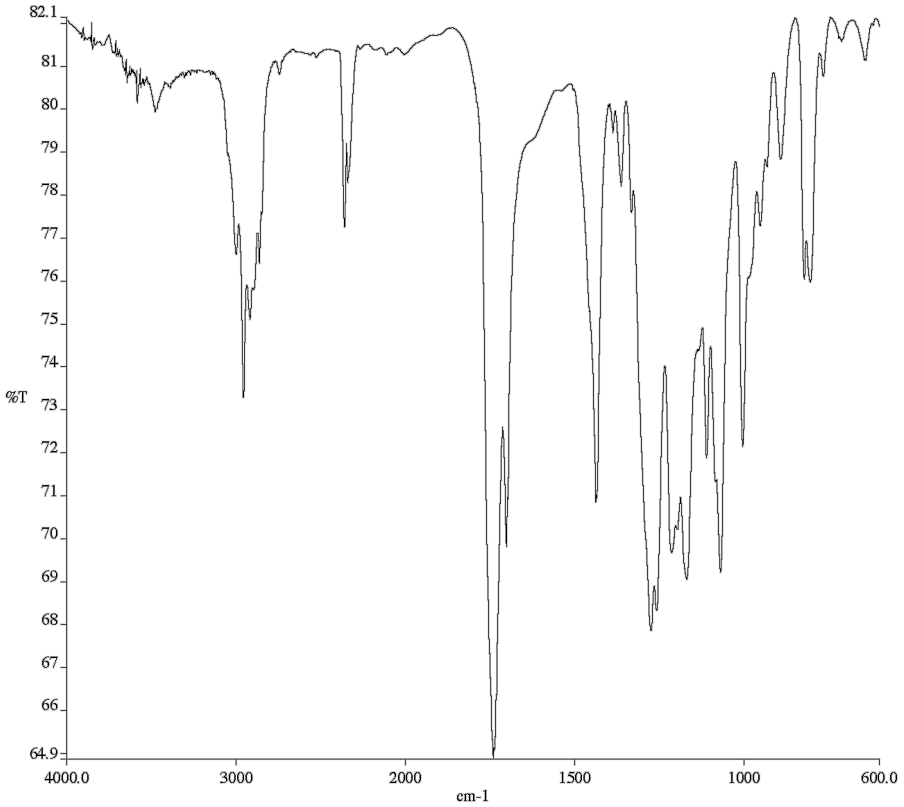


Figure A8.110. Infrared spectrum (Thin Film, NaCl) of compound **175d**.

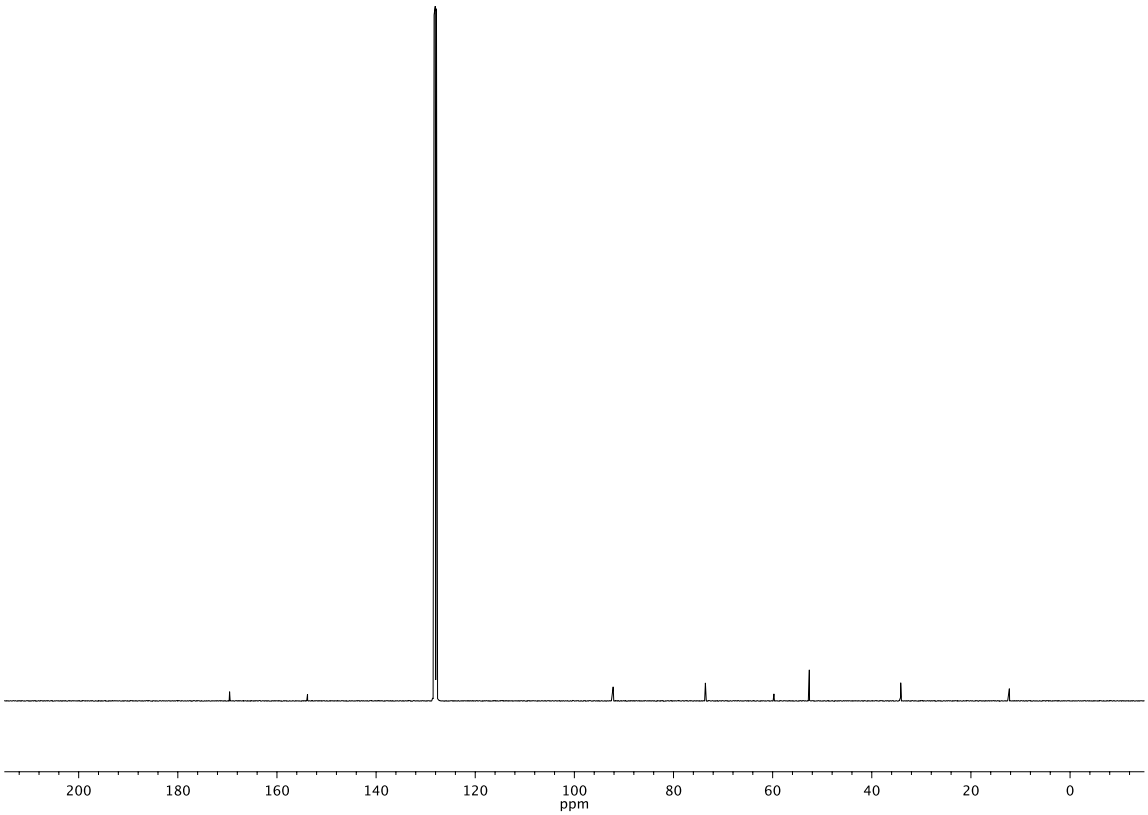


Figure A8.111. ^{13}C NMR (101 MHz, C_6D_6) of compound **175d**.

Figure A8.112. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **174e**.

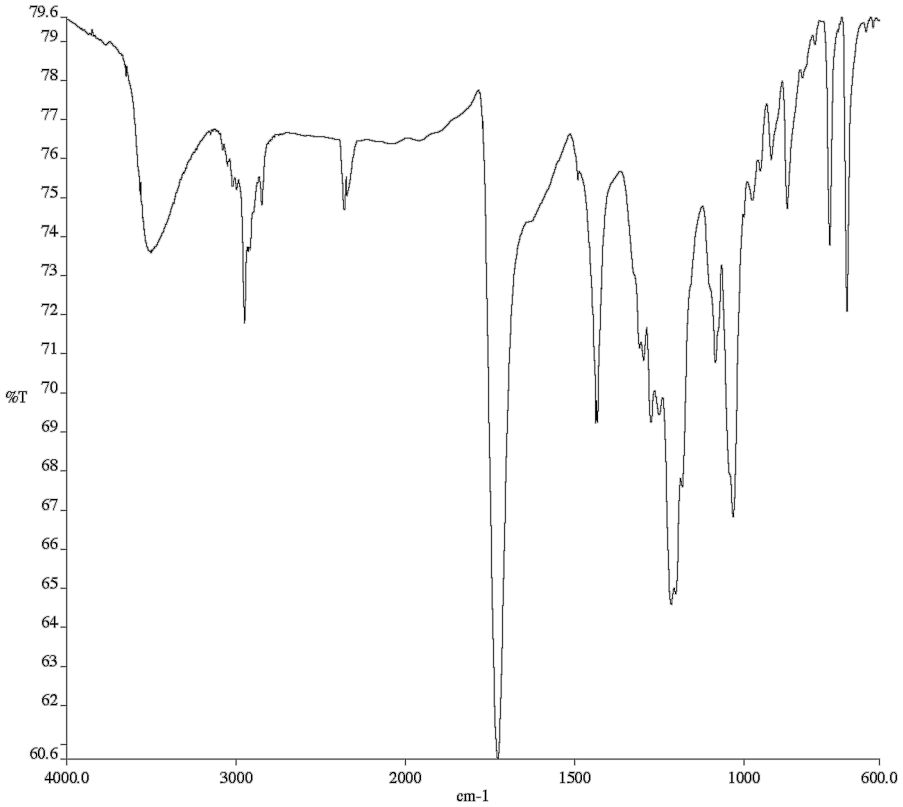


Figure A8.113. Infrared spectrum (Thin Film, NaCl) of compound **174e**.

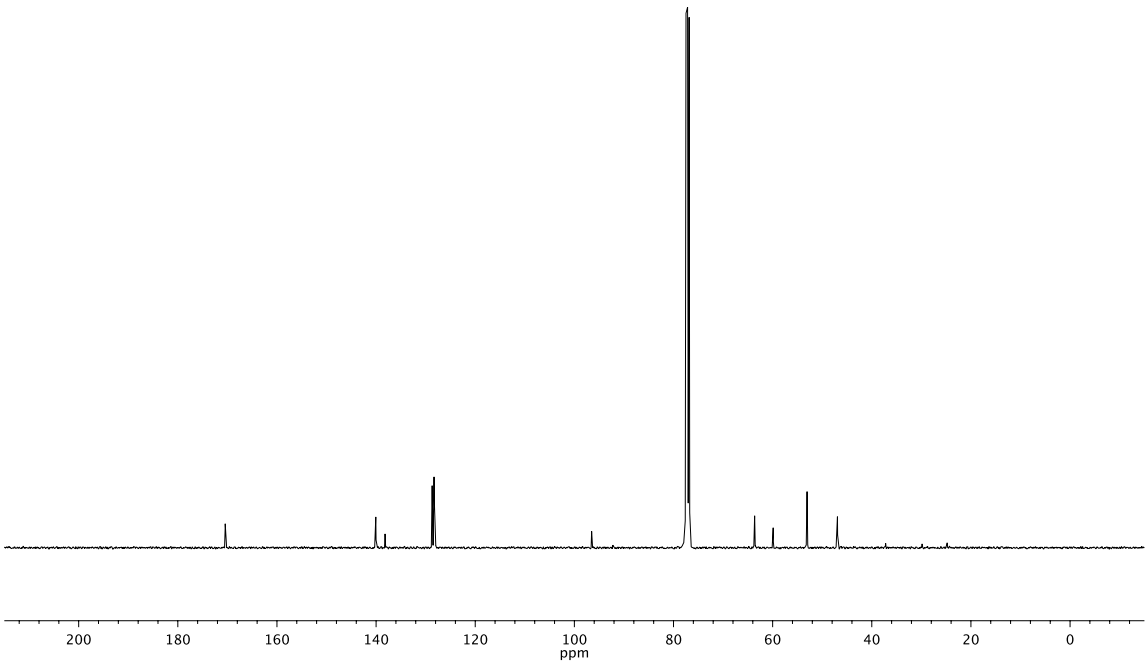


Figure A8.114. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **174e**.

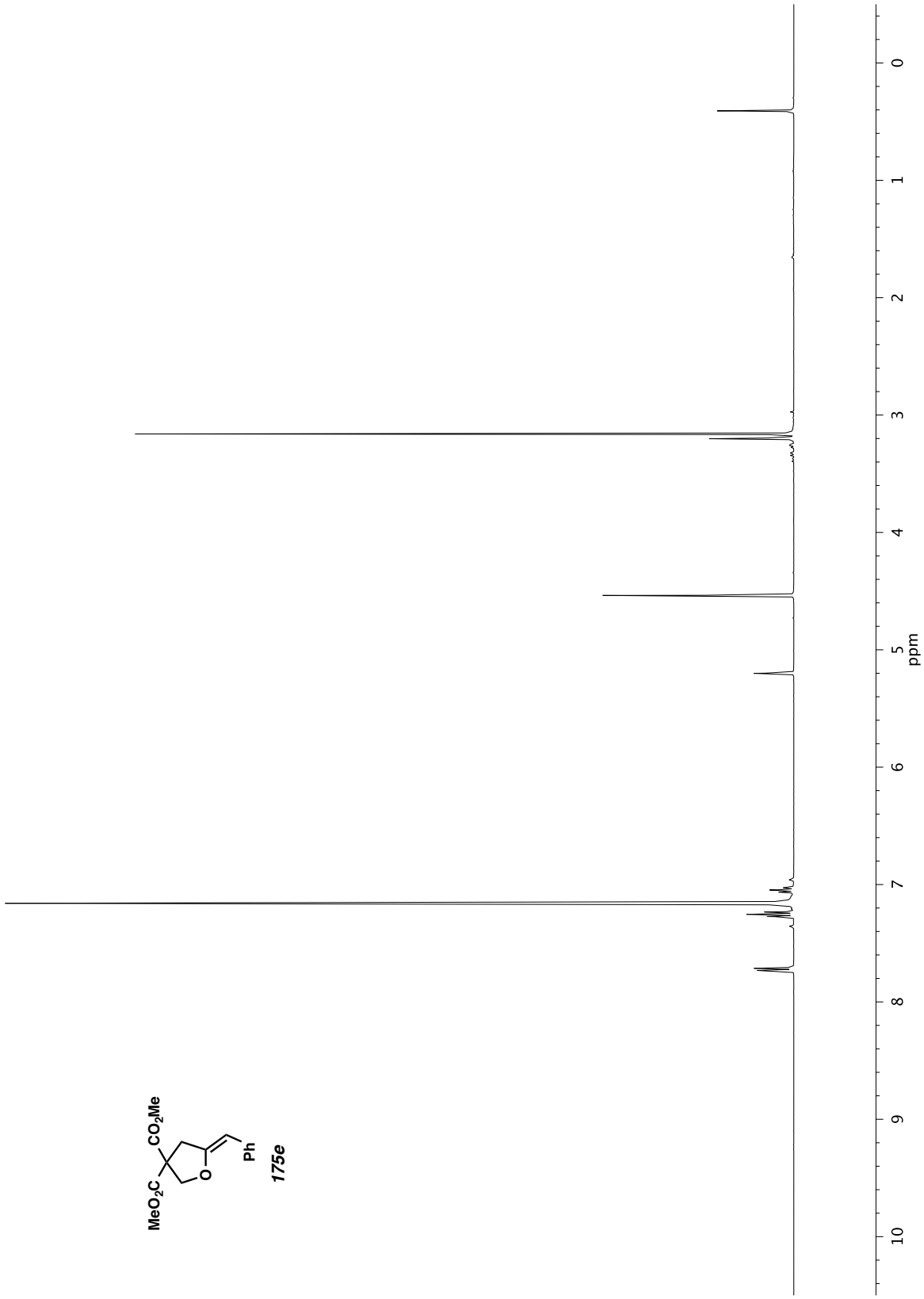


Figure A8.115. ^{1}H NMR (400 MHz, C_6D_6) of compound **175e**.

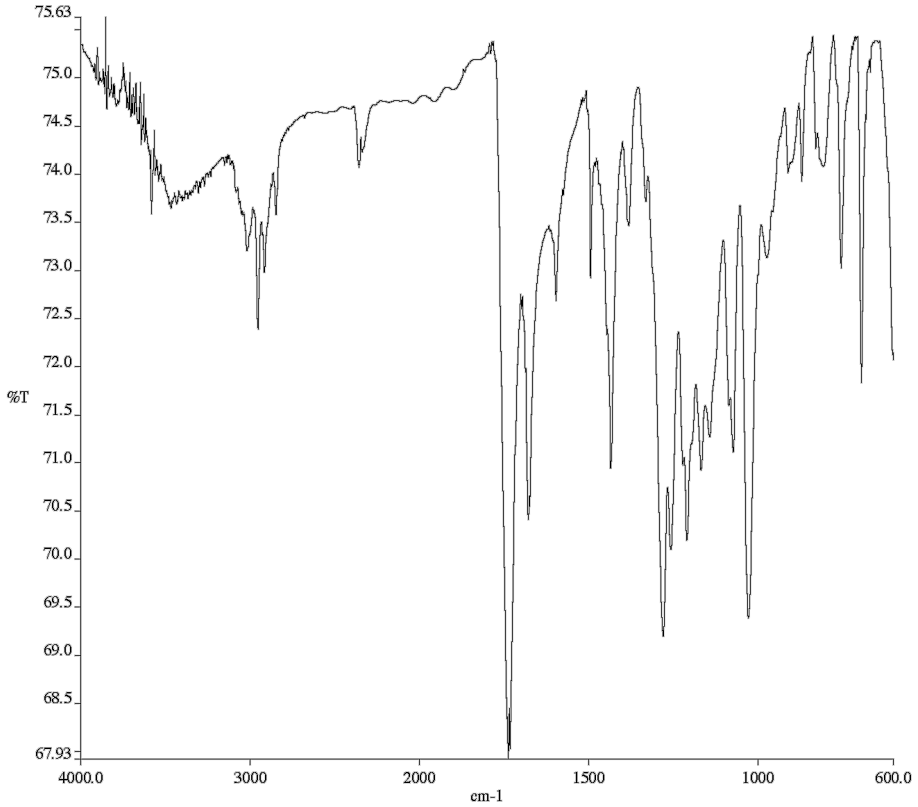


Figure A8.116. Infrared spectrum (Thin Film, NaCl) of compound **175e**.

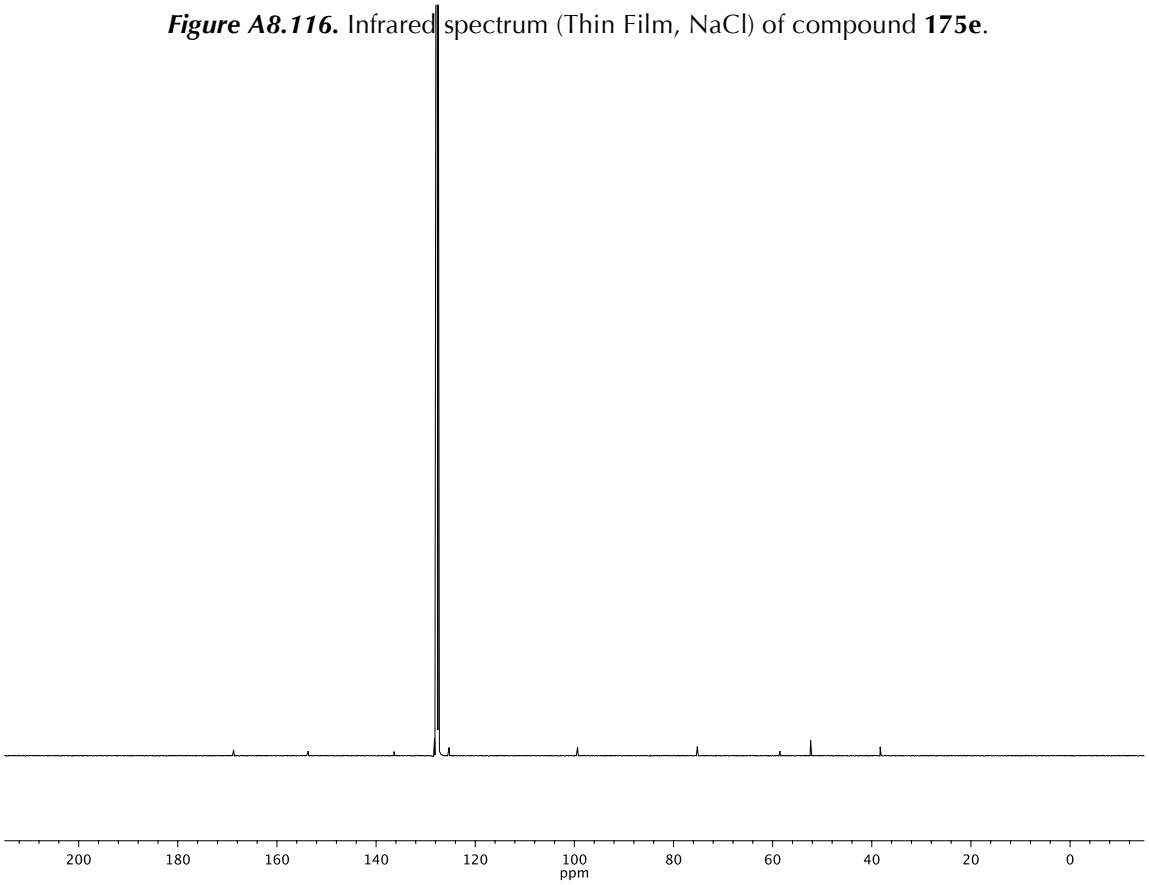


Figure A8.117. ^{13}C NMR (101 MHz, C_6D_6) of compound **175e**.

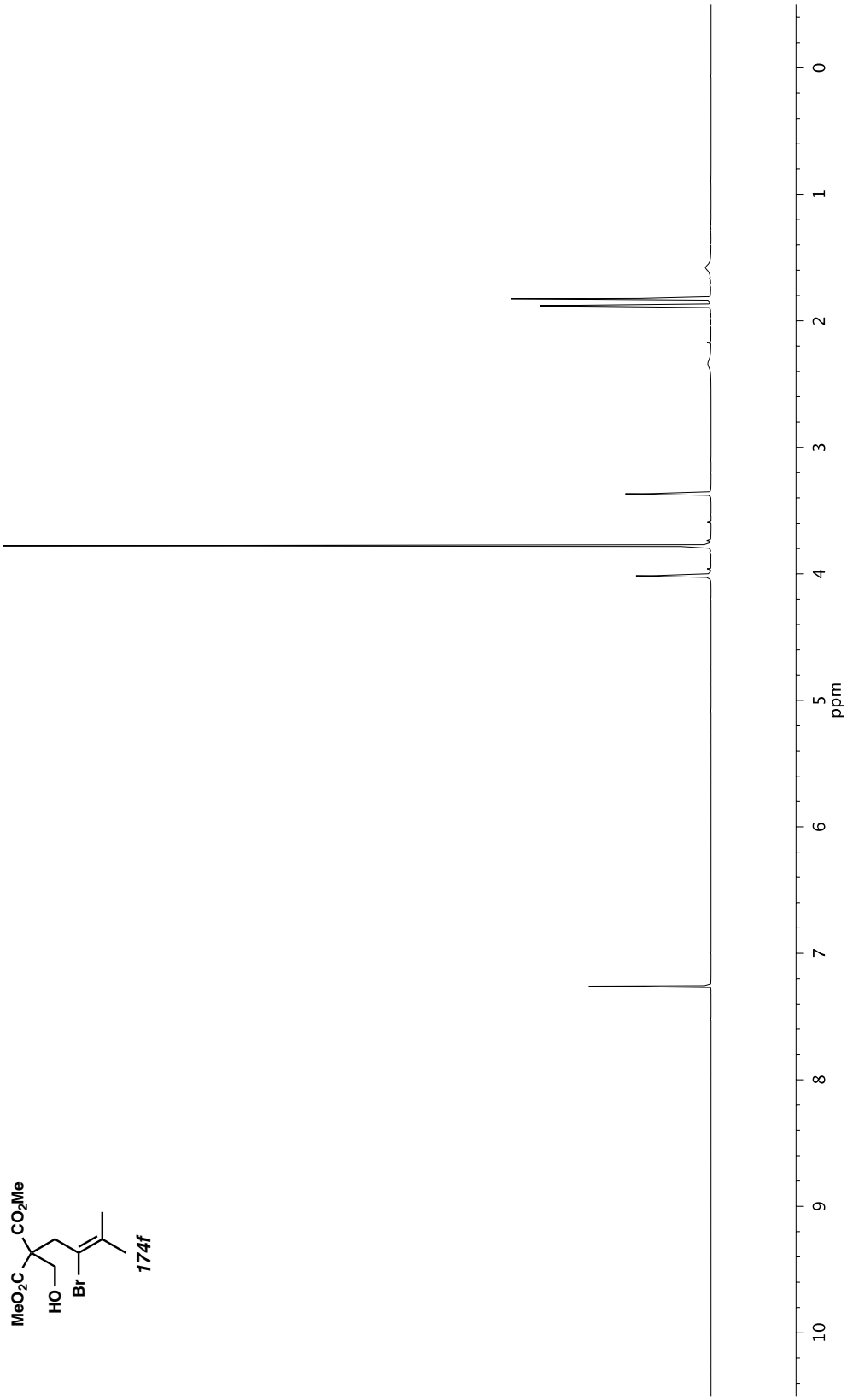


Figure A8.118. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **174f**.

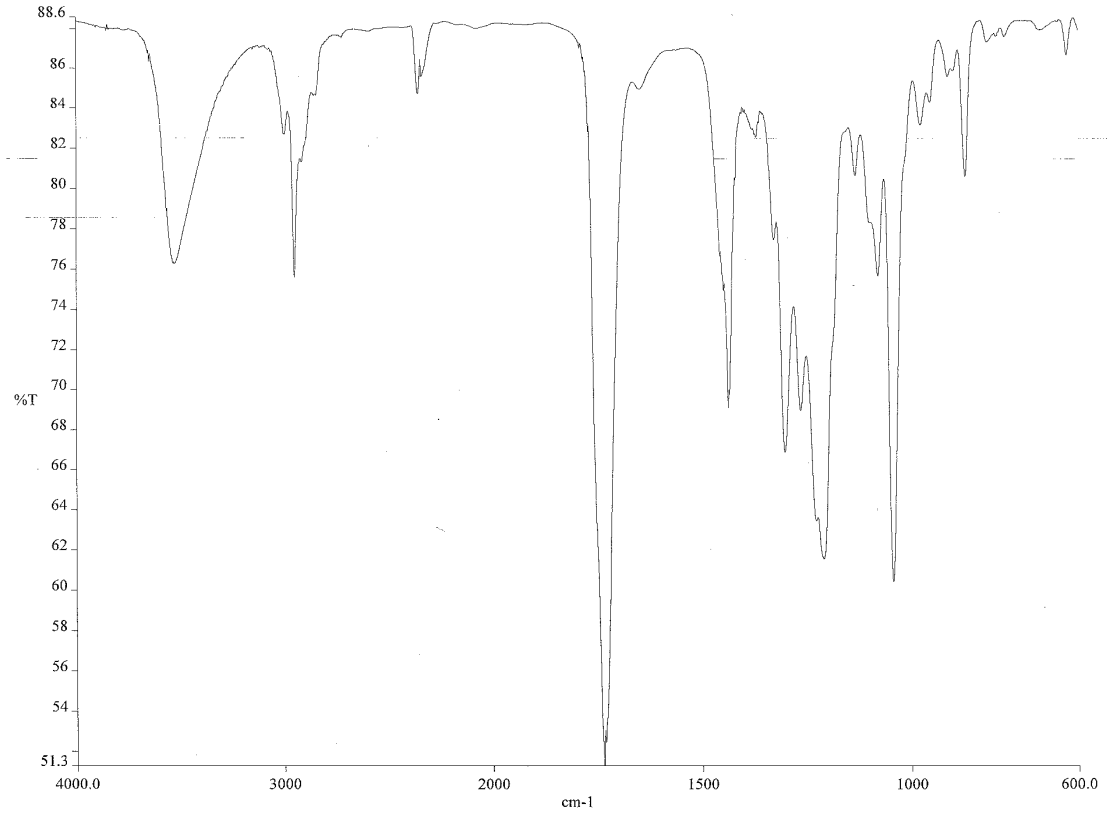


Figure A8.119. Infrared spectrum (Thin Film, NaCl) of compound **174f**.

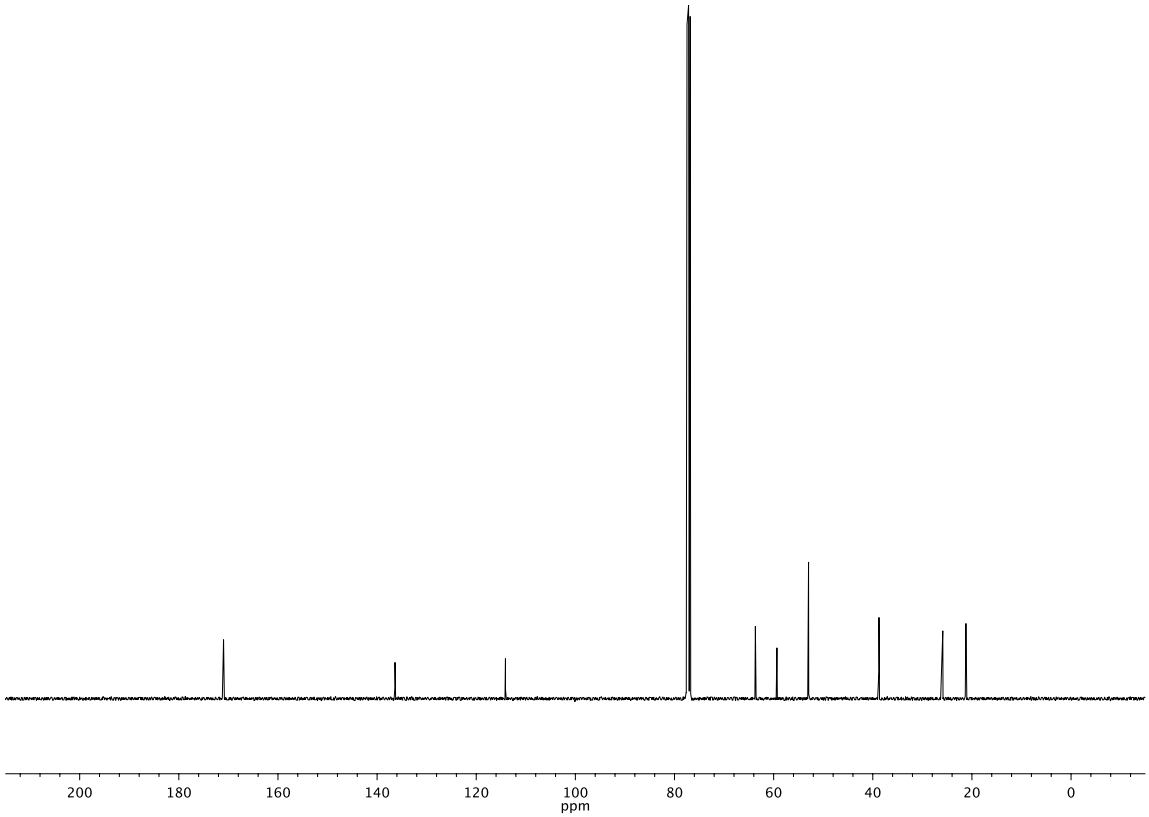


Figure A8.120. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **174f**.

Figure A8.121. ^{1}H NMR (500 MHz, C_6D_6) of compound **175f**.

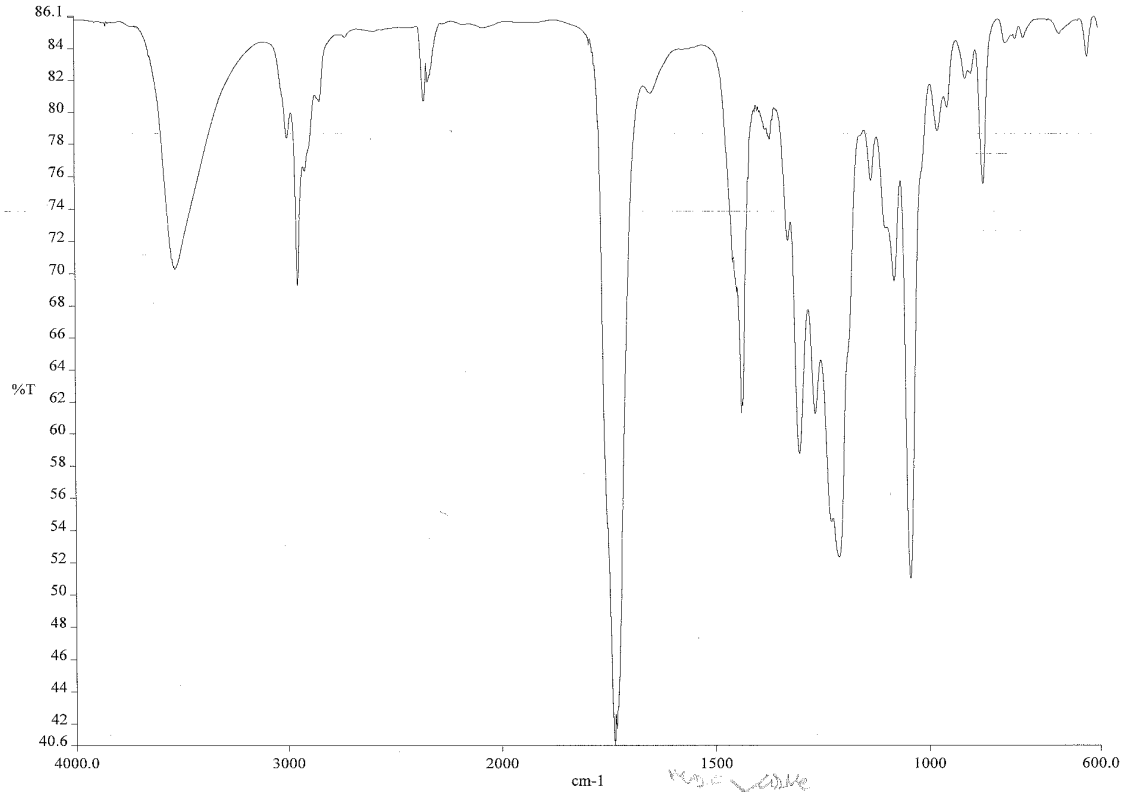


Figure A8.122. Infrared spectrum (Thin Film, NaCl) of compound **175f**.

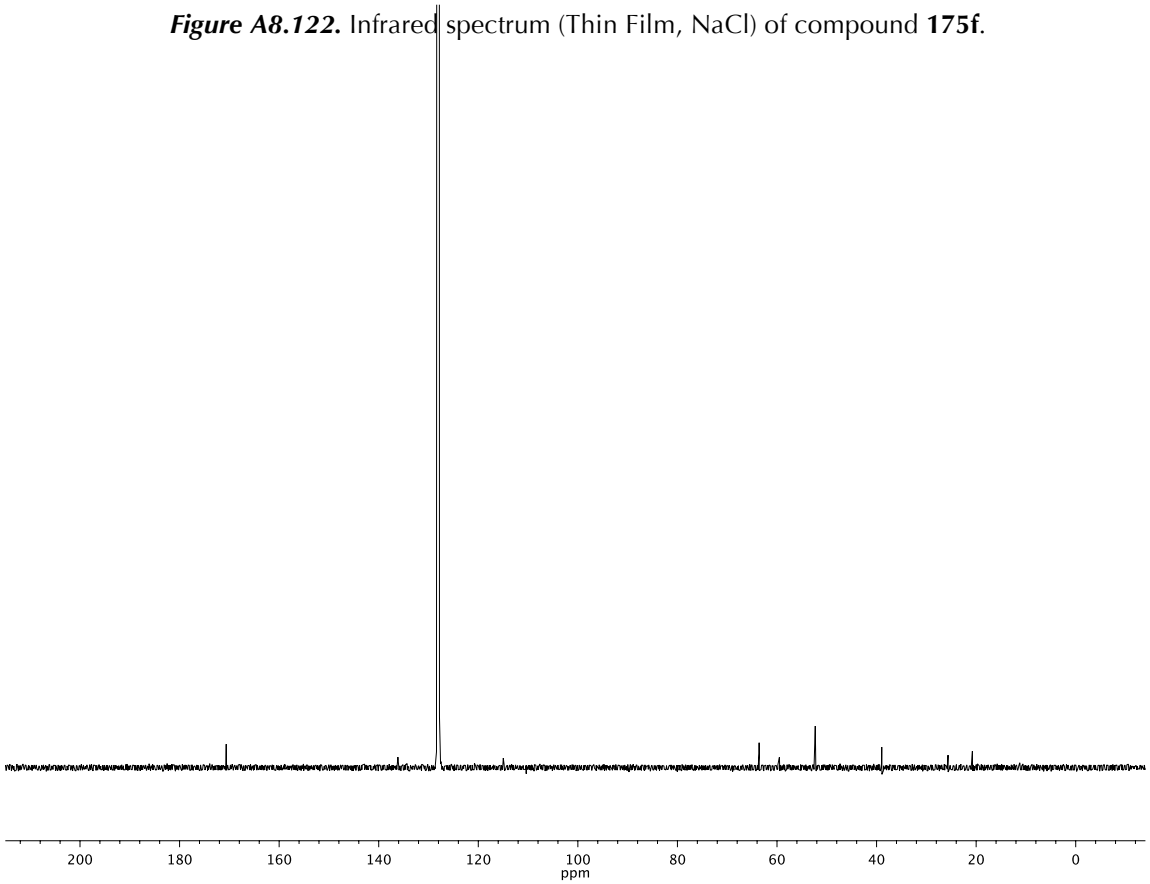


Figure A8.123. ^{13}C NMR (126 MHz, C_6D_6) of compound **175f**.

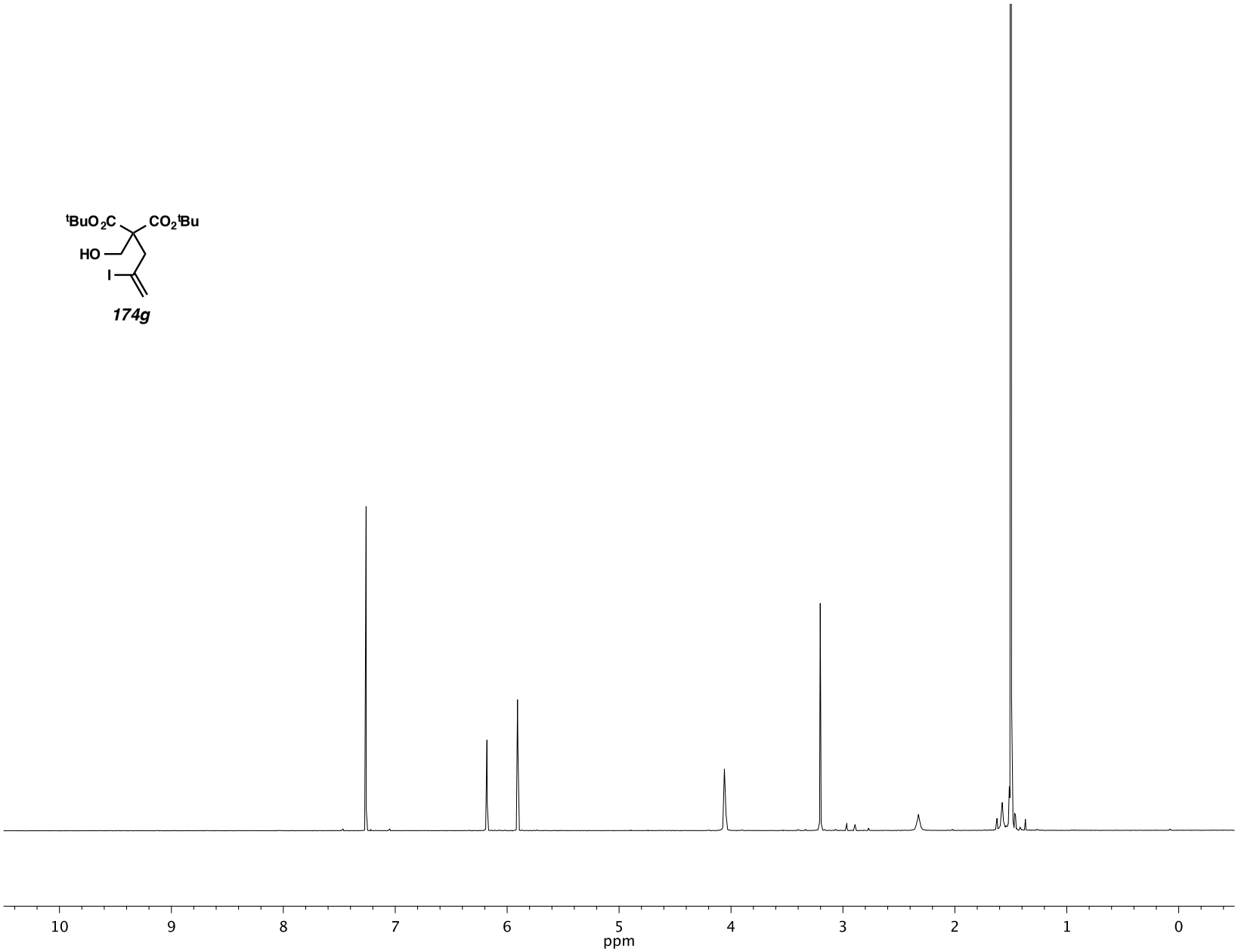


Figure A8.124. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **174g**.

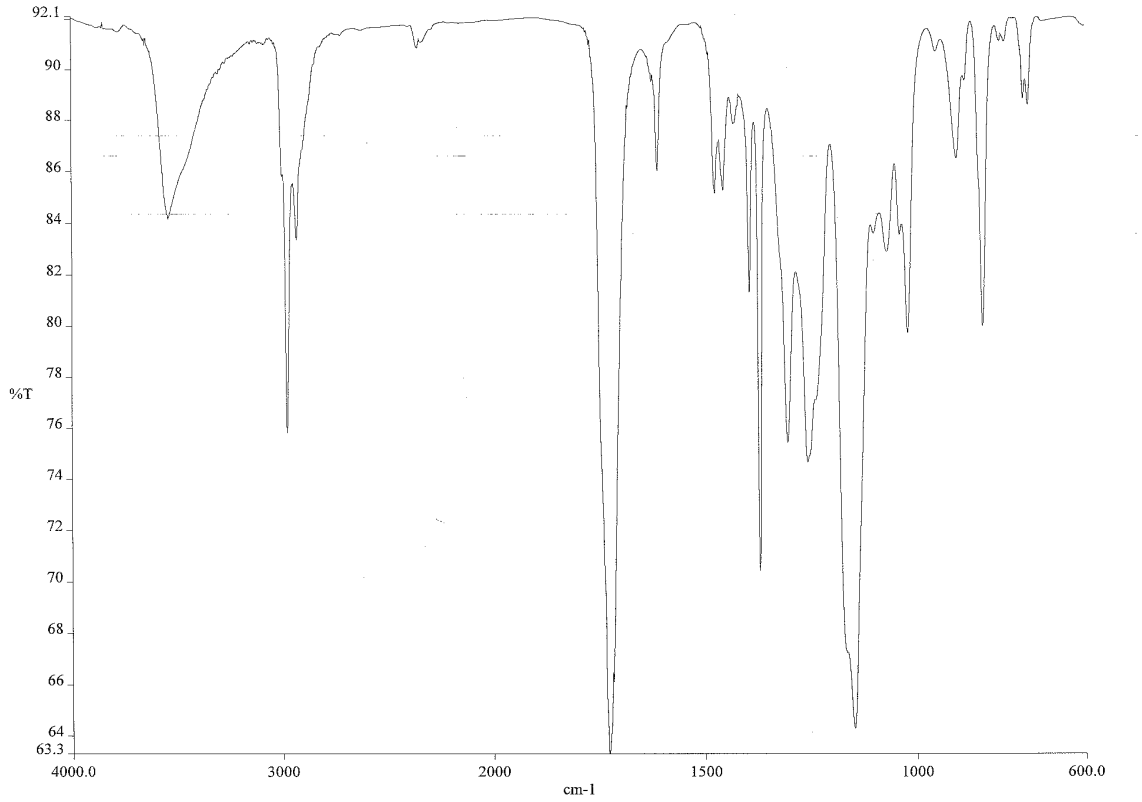


Figure A8.125. Infrared spectrum (Thin Film, NaCl) of compound **174g**.

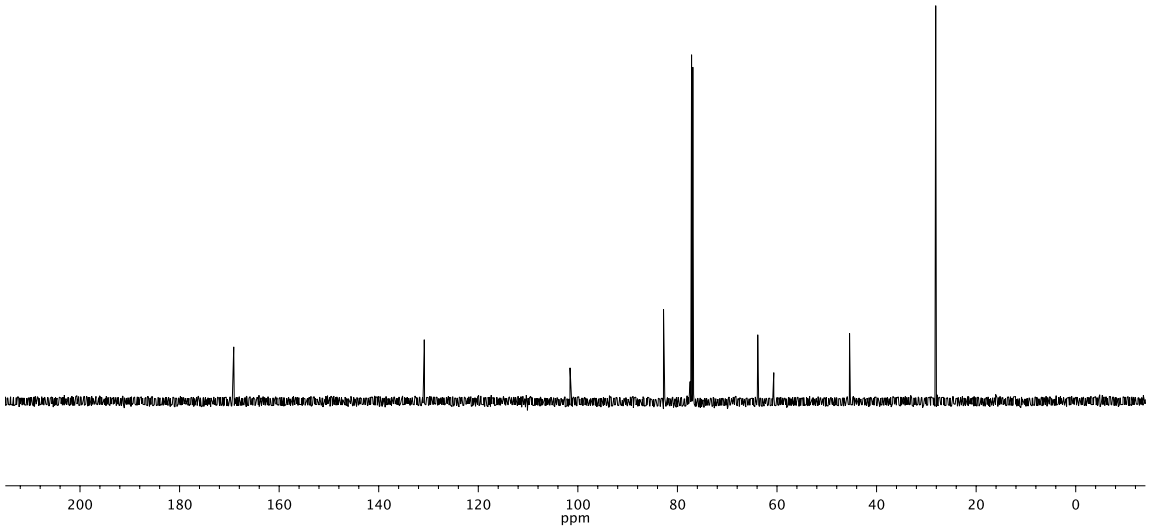


Figure A8.126. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **174g**.

Figure A8.127. ^{1}H NMR (500 MHz, C_6D_6) of compound **175g**.

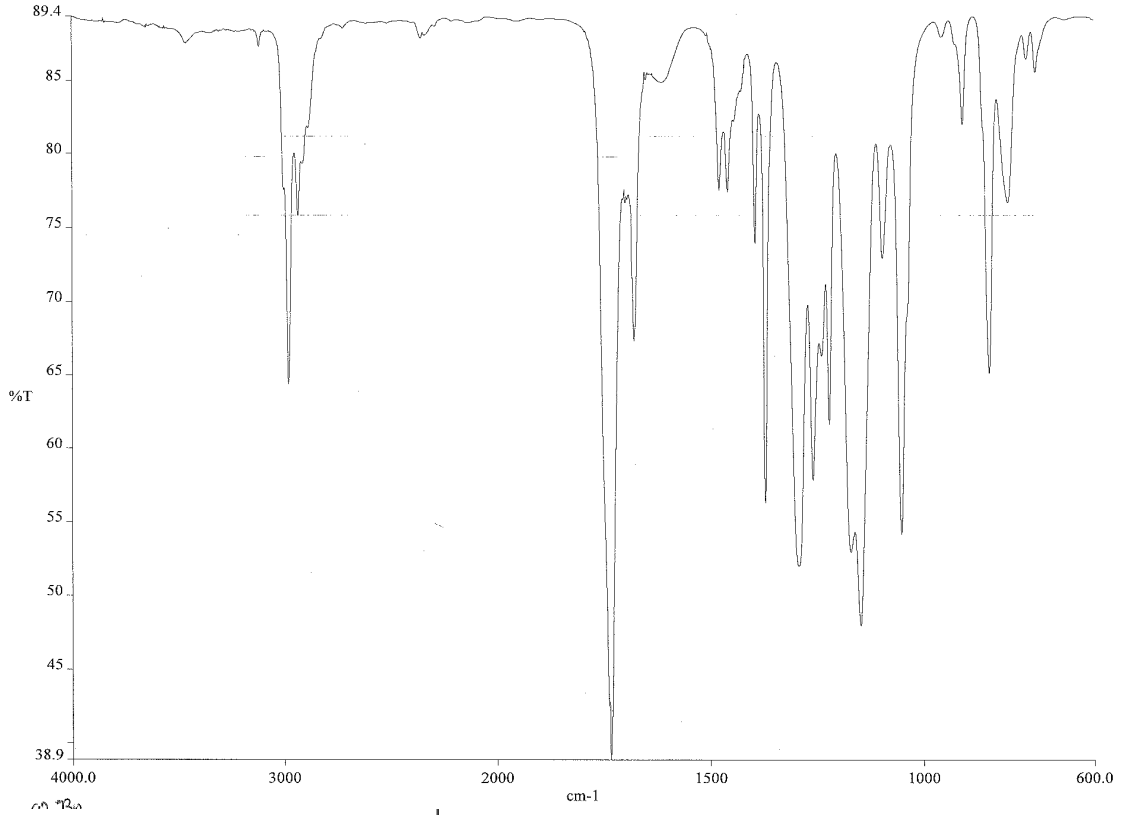


Figure A8.128. Infrared spectrum (Thin Film, NaCl) of compound **175g**.

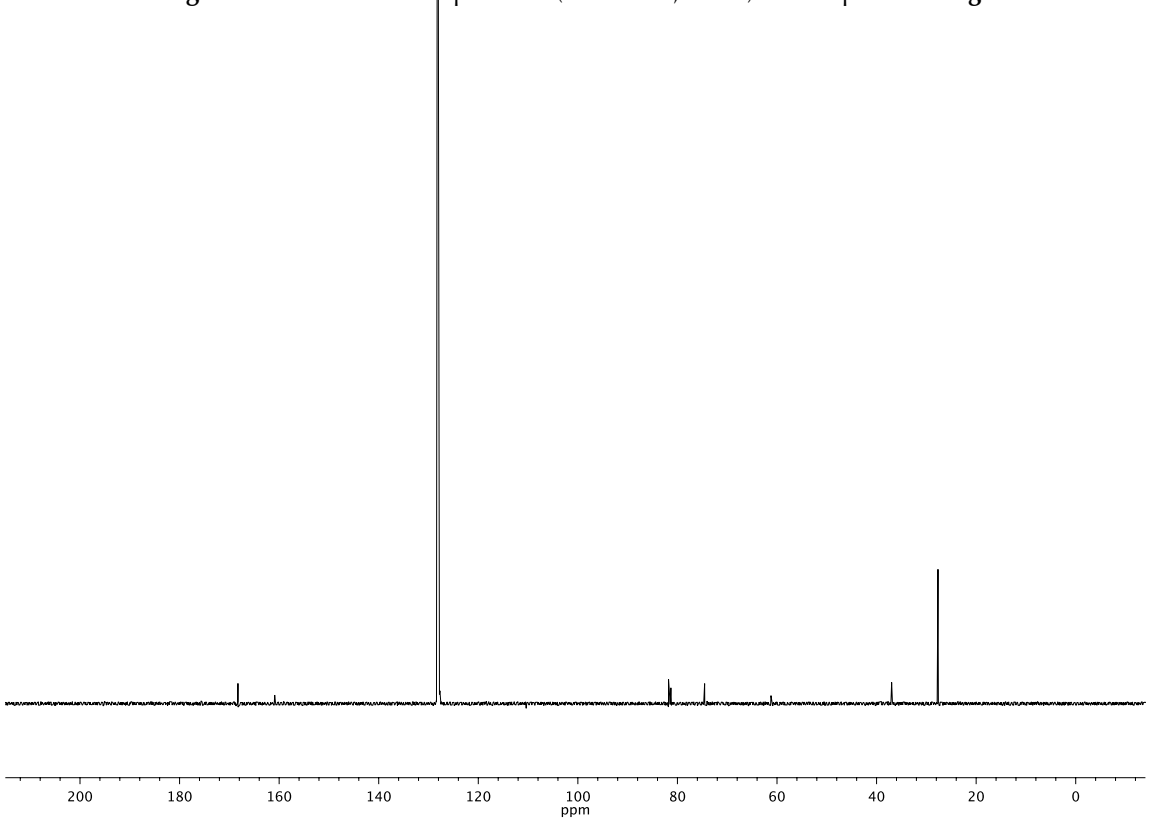


Figure A8.129. ^{13}C NMR (126 MHz, C_6D_6) of compound **175g**.

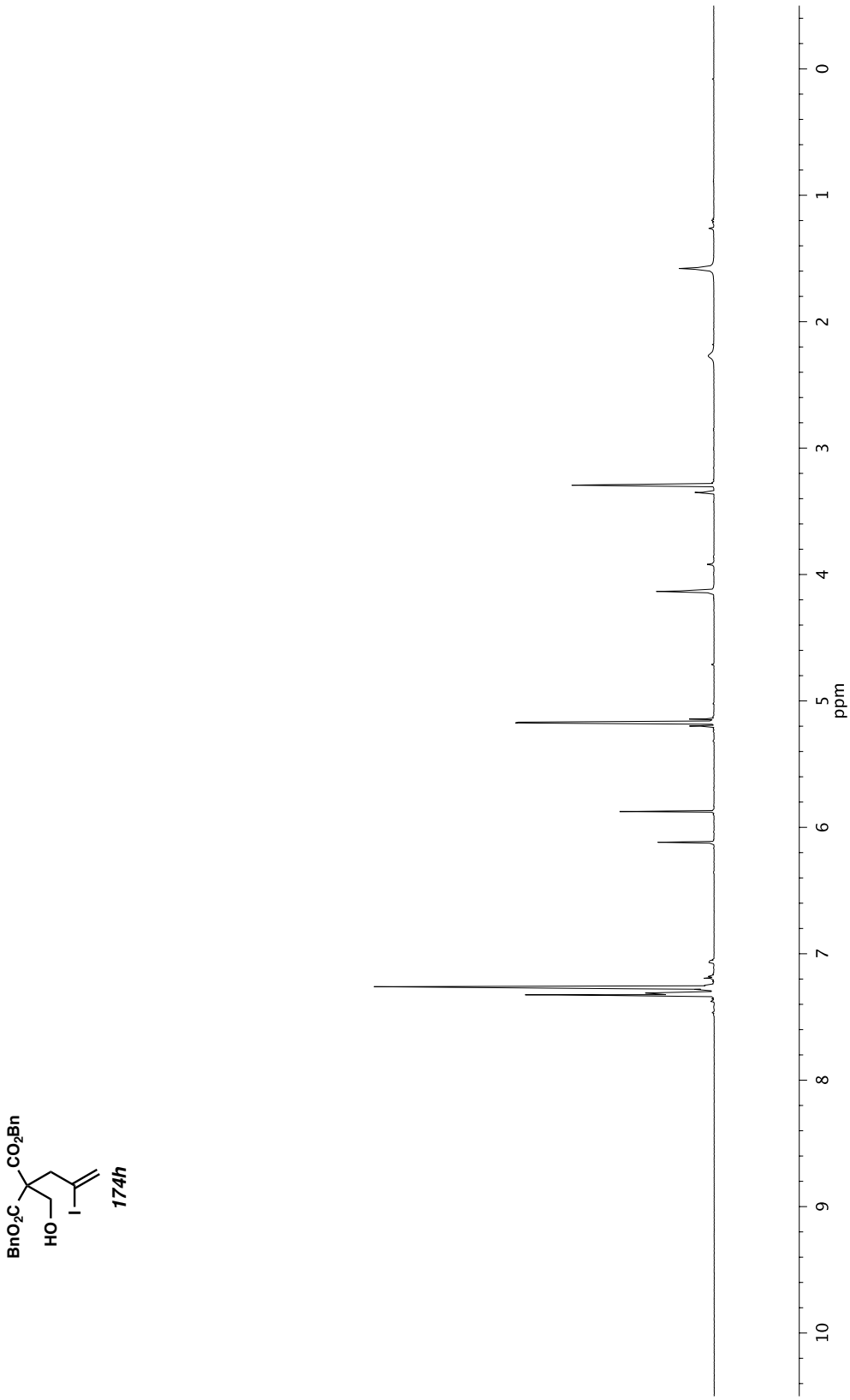


Figure A8.130. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **174h**.

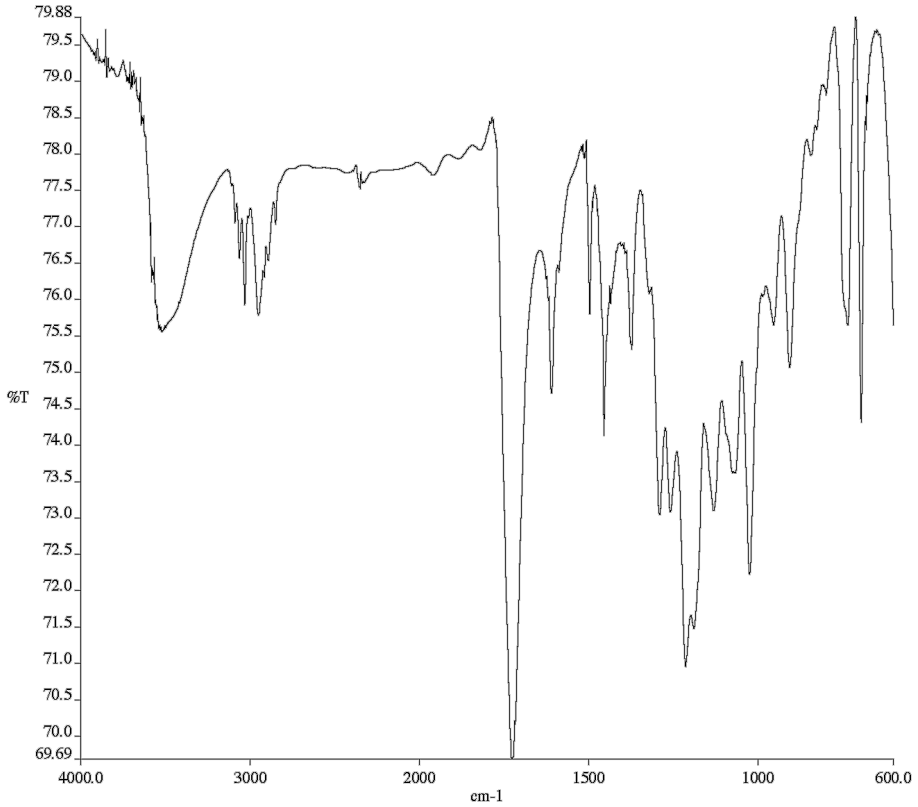


Figure A8.131. Infrared spectrum (Thin Film, NaCl) of compound **174h**.

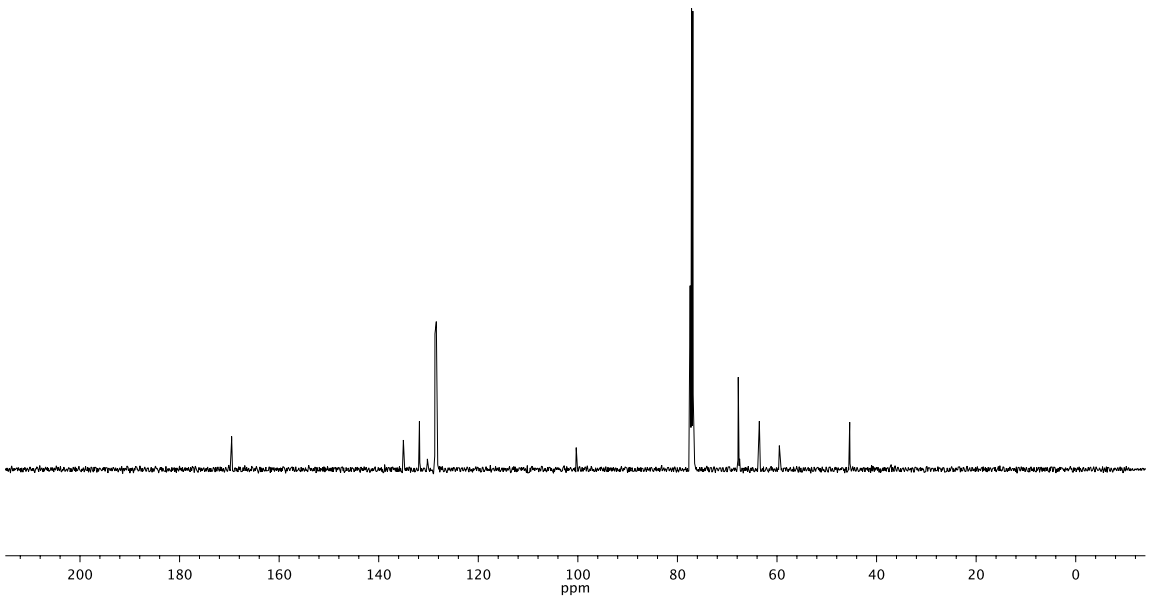


Figure A8.132. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **174h**.

Figure A8.133. ^{1}H NMR (600 MHz, C_6D_6) of compound **175h**.

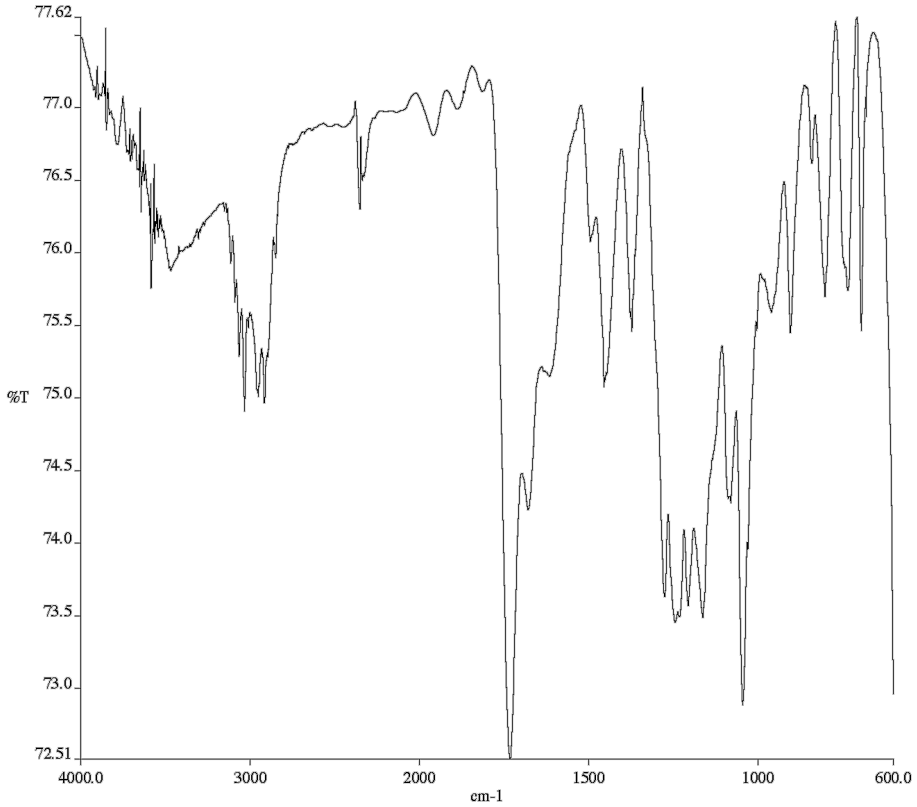


Figure A8.134. Infrared spectrum (Thin Film, NaCl) of compound **175h**.

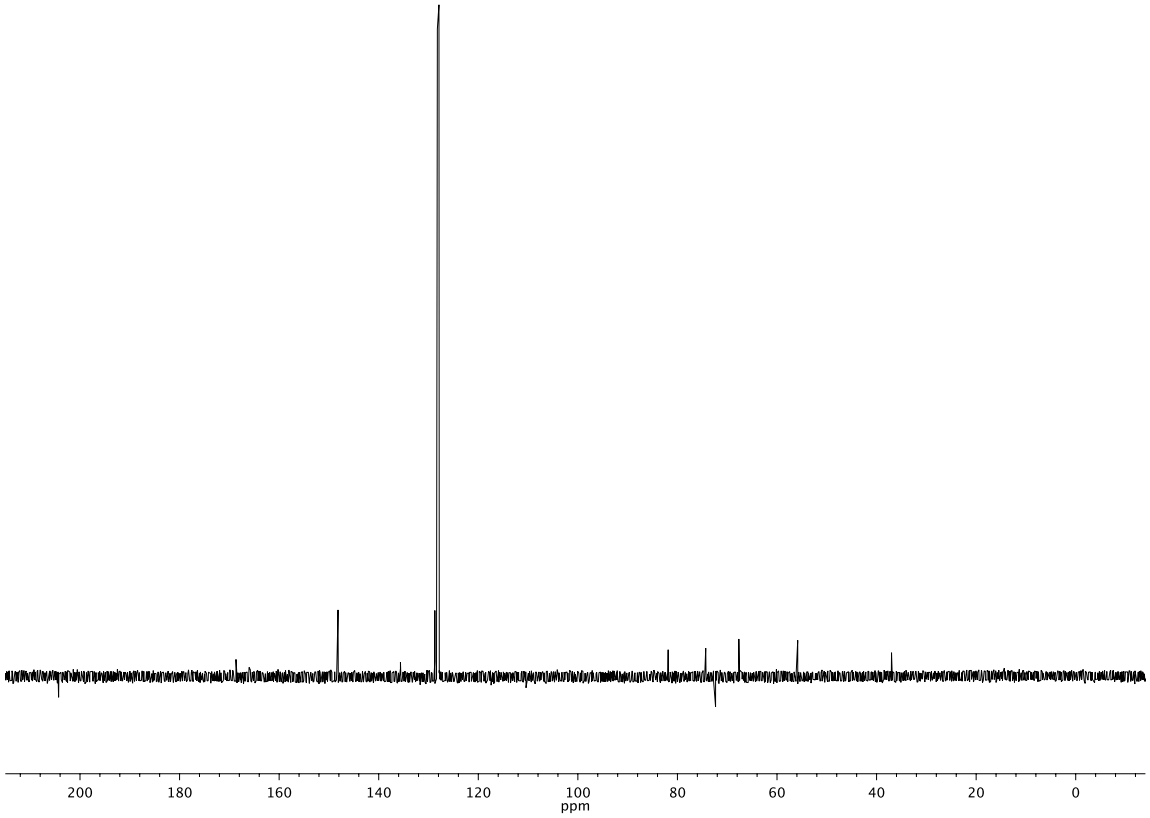


Figure A8.135. ^{13}C NMR (151 MHz, C_6D_6) of compound **175h**.

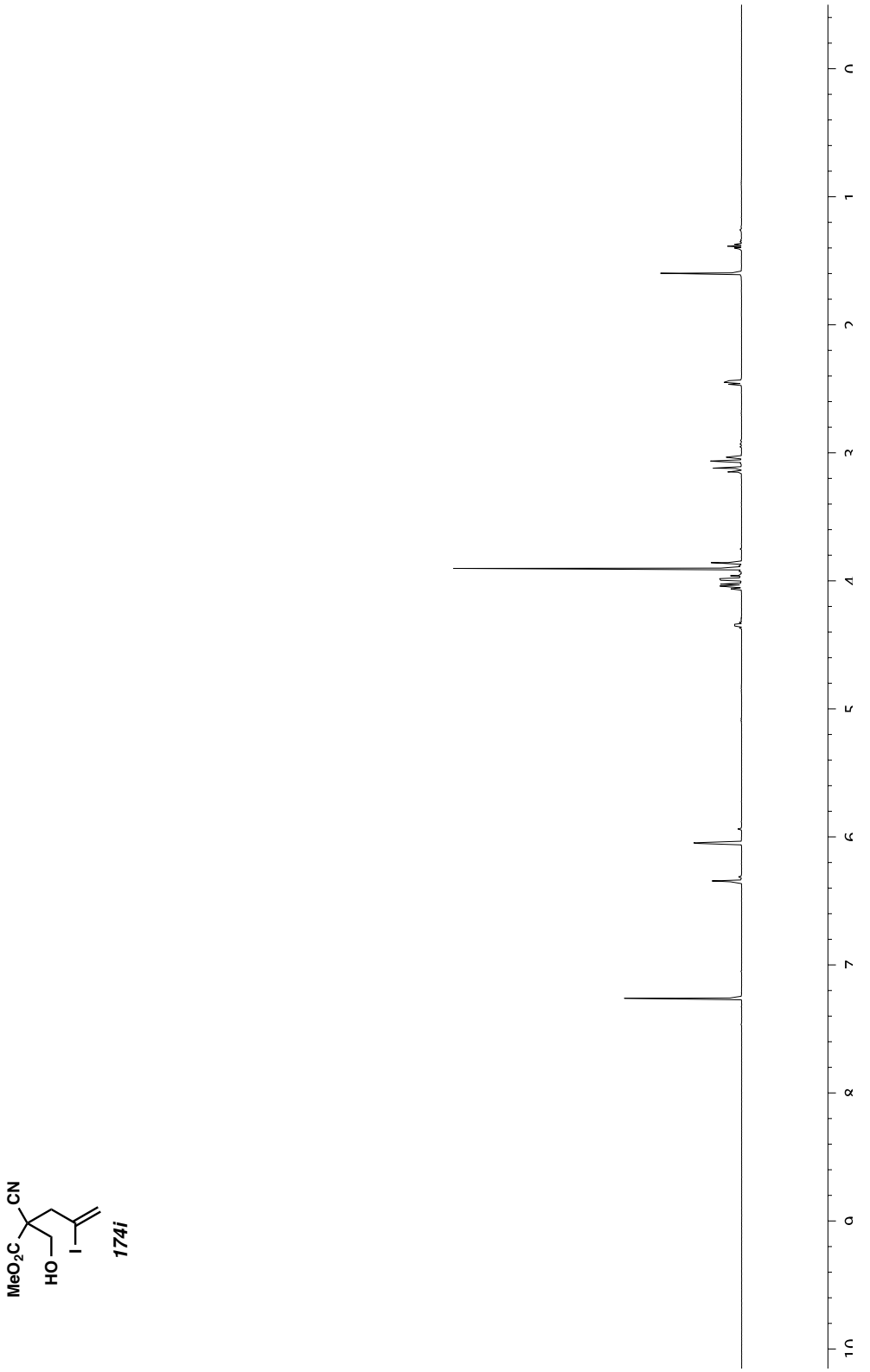


Figure A8.136. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **174i**.

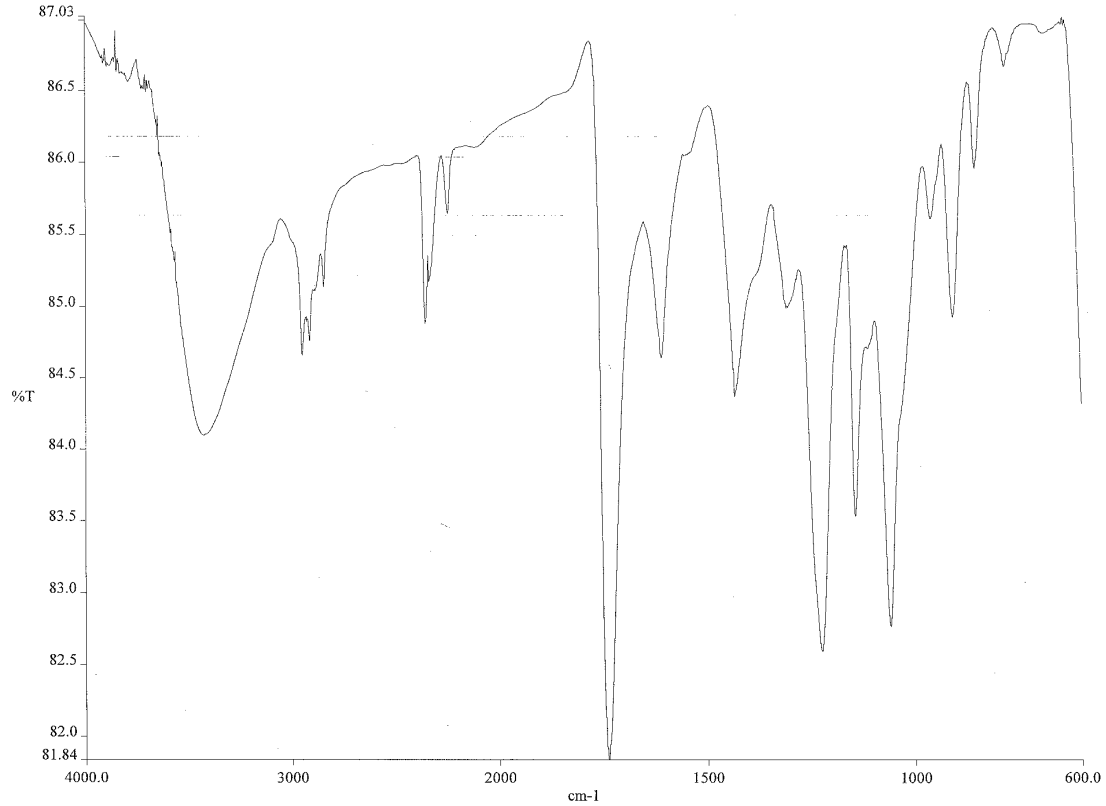


Figure A8.137. Infrared spectrum (Thin Film, NaCl) of compound **174i**.

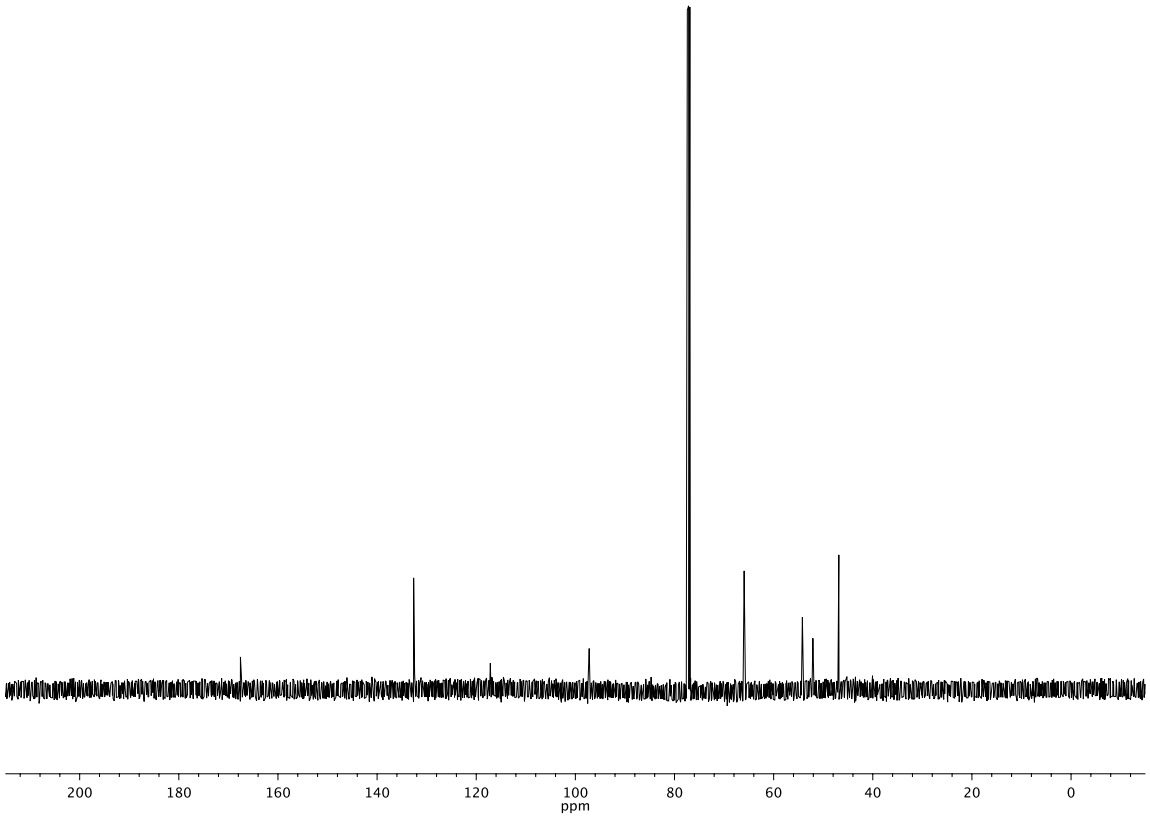


Figure A8.138. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **174i**.

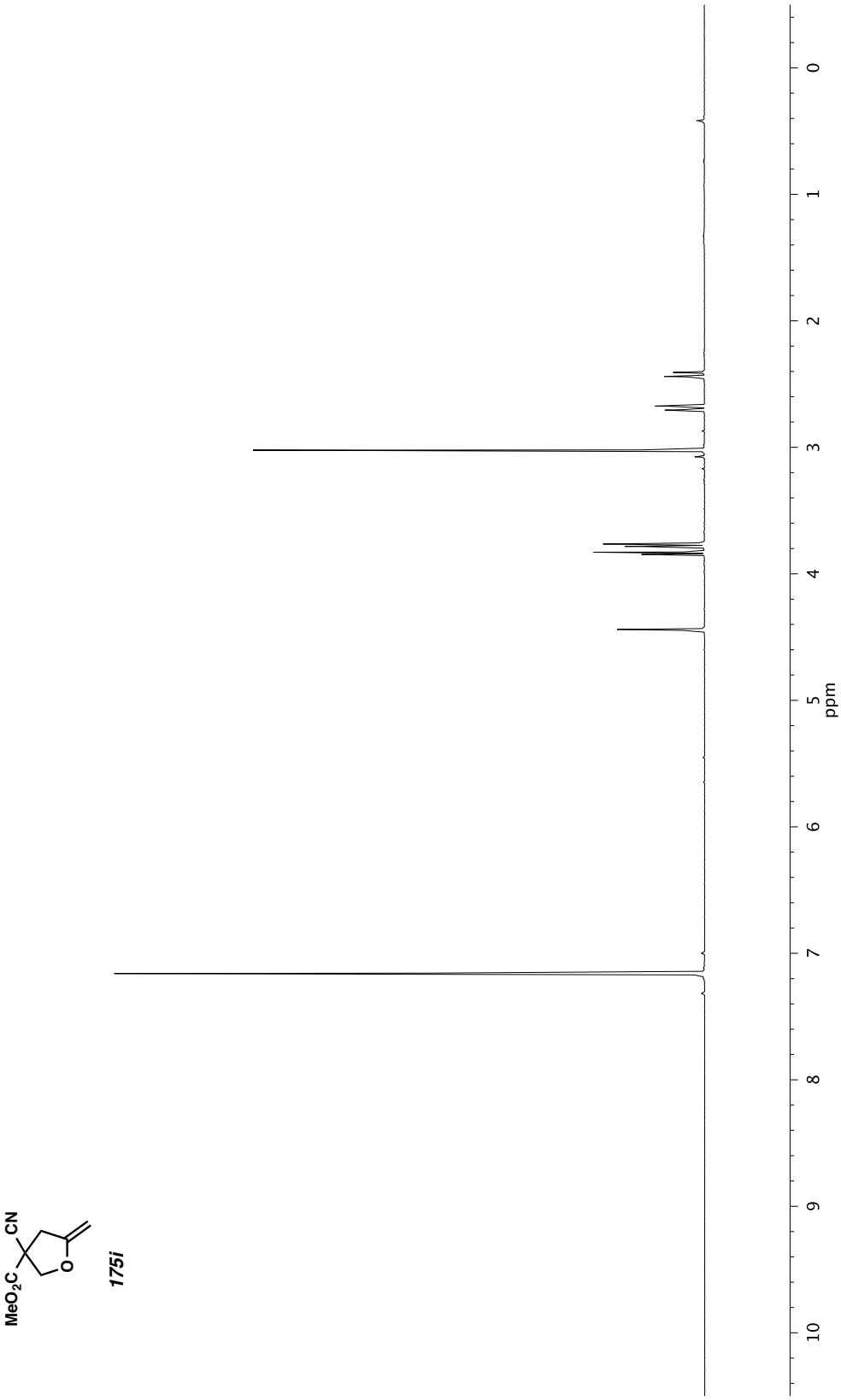


Figure A8.139. ^{1}H NMR (500 MHz, C_6D_6) of compound **175i**.

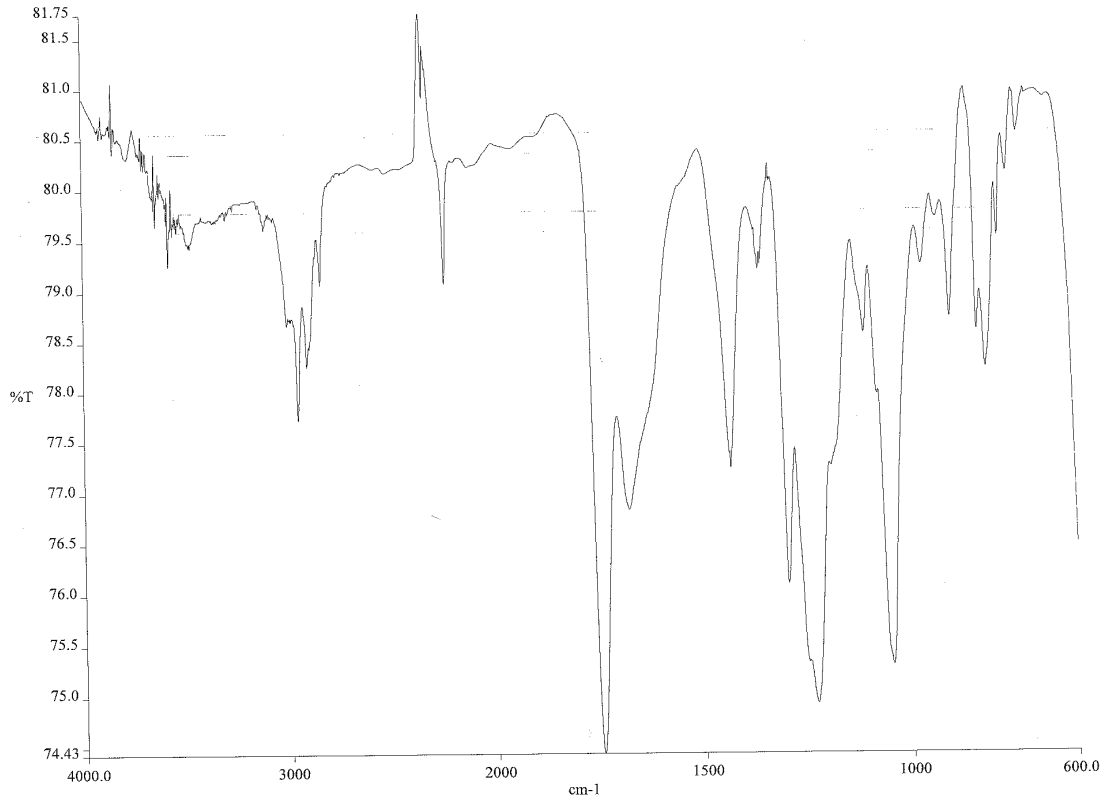


Figure A8.140. Infrared spectrum (Thin Film, NaCl) of compound **175i**.

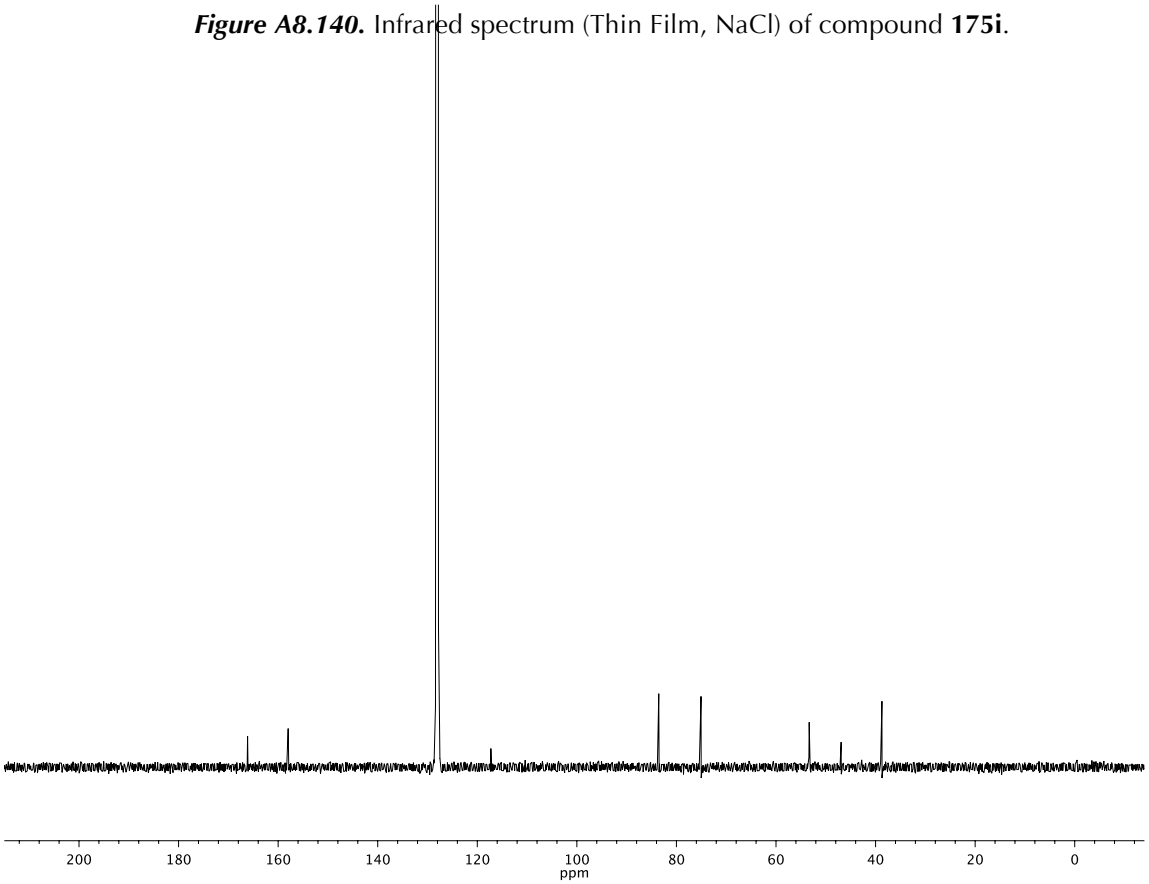
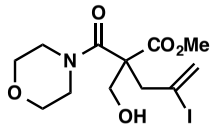


Figure A8.141. ^{13}C NMR (126 MHz, C_6D_6) of compound **175i**.



174j

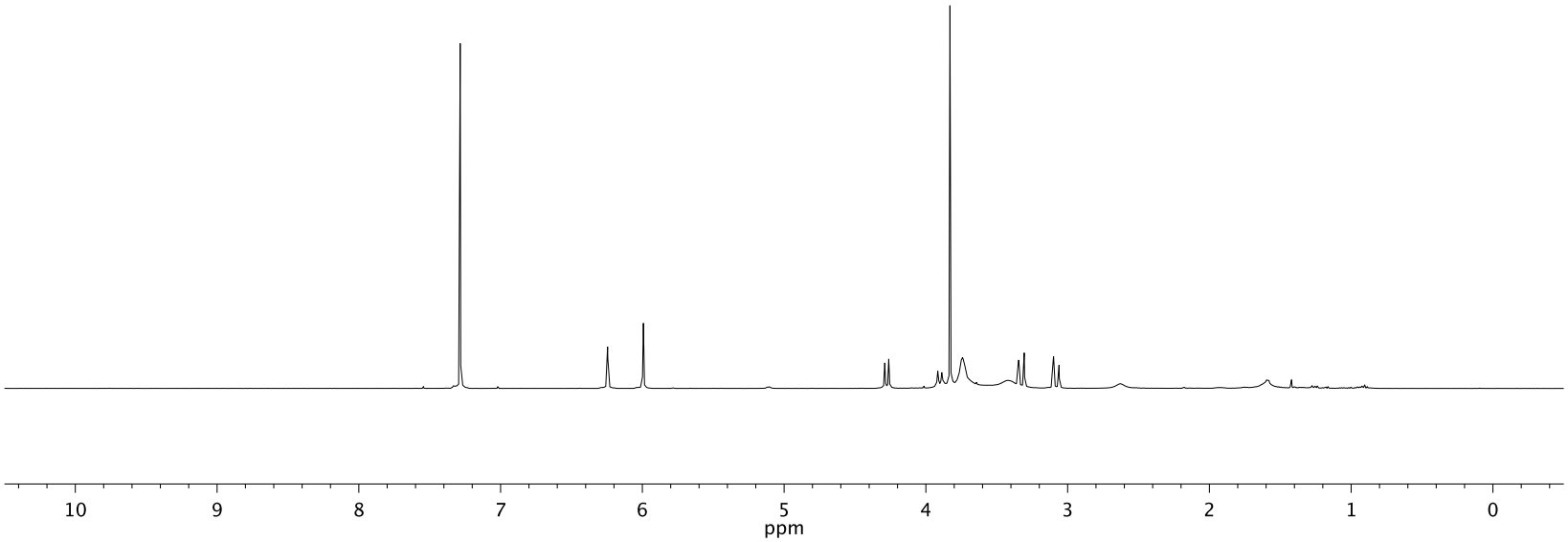


Figure A8.142. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **174j**.

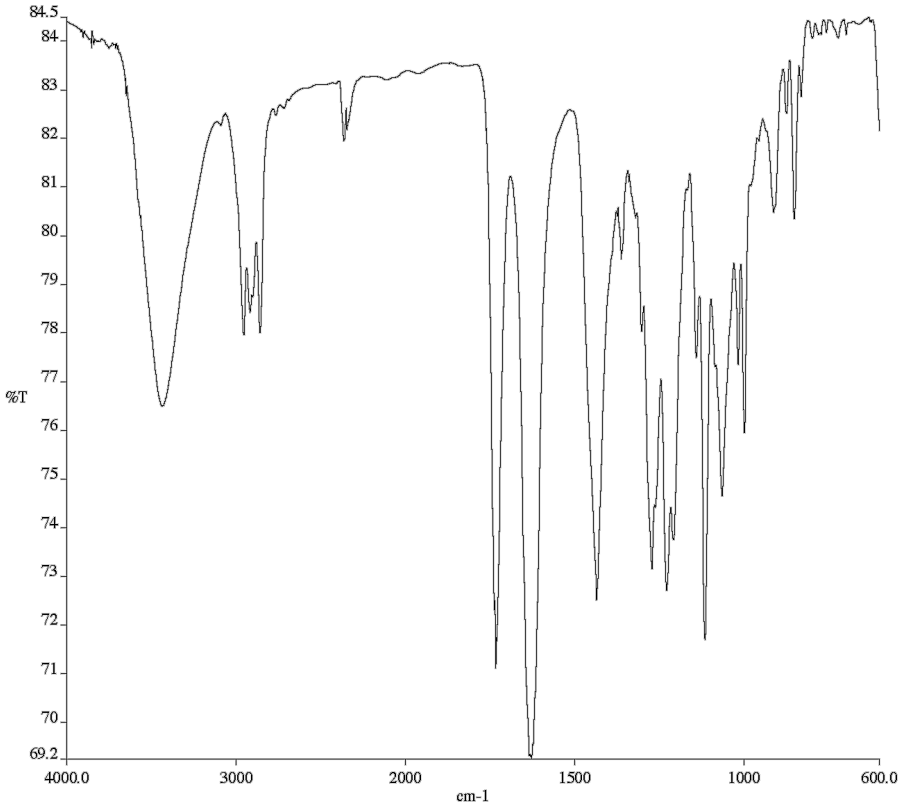


Figure A8.143. Infrared spectrum (Thin Film, NaCl) of compound **174j**

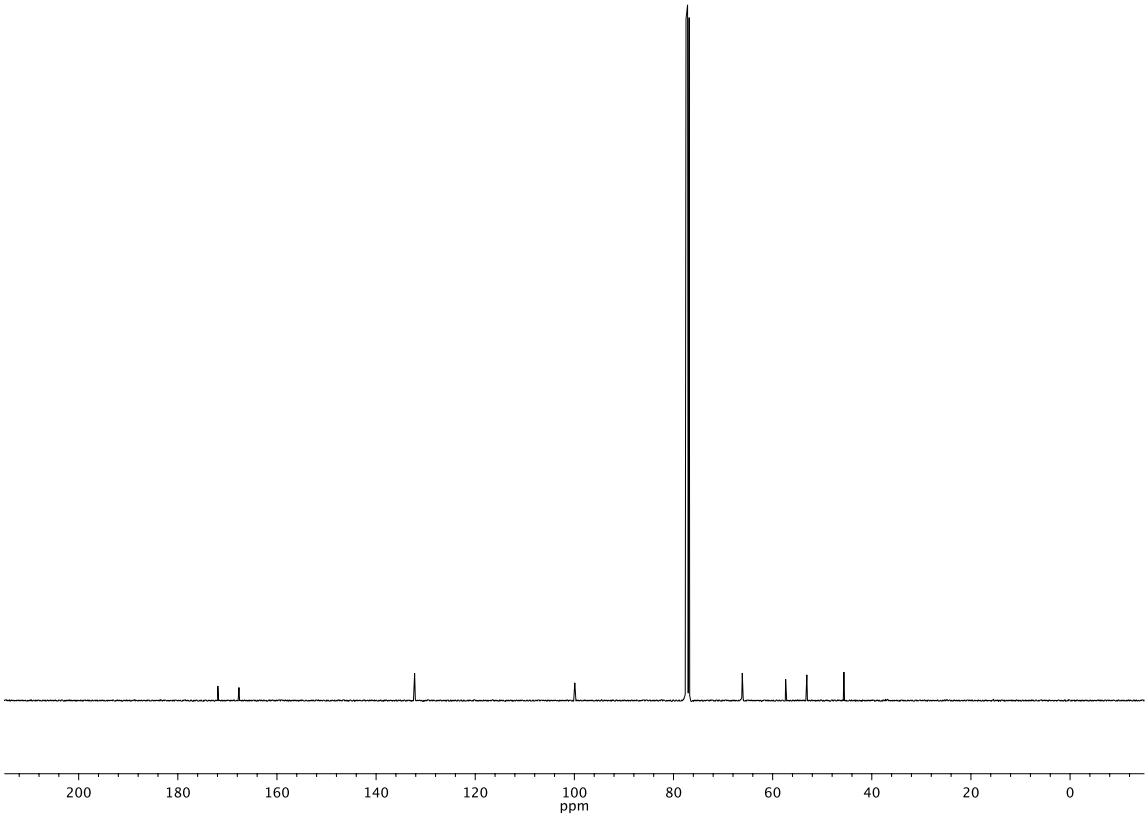
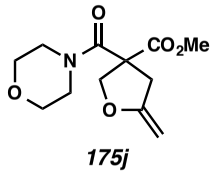


Figure A8.144. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **174j**.



175j

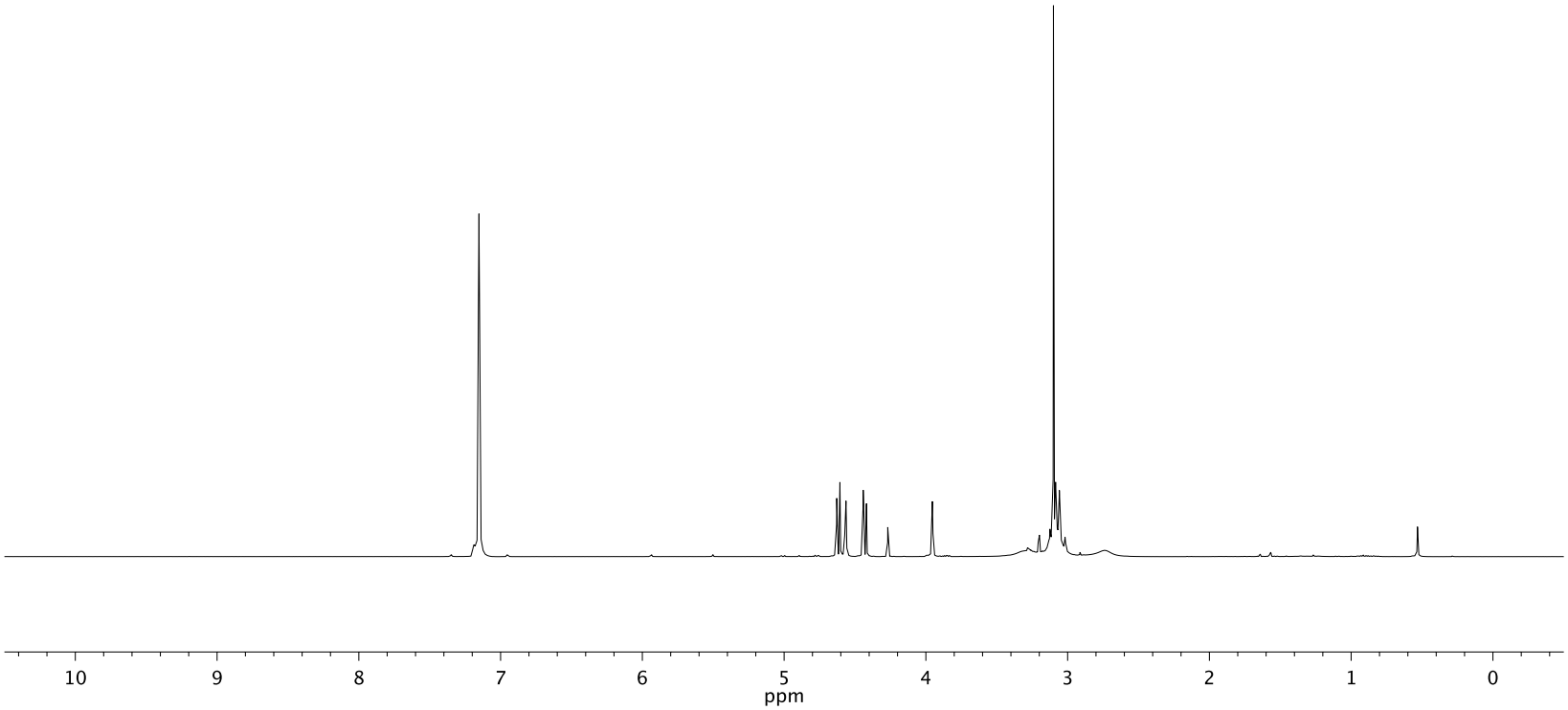


Figure A8.145. ^{1}H NMR (500 MHz, C_6D_6) of compound **175j**.

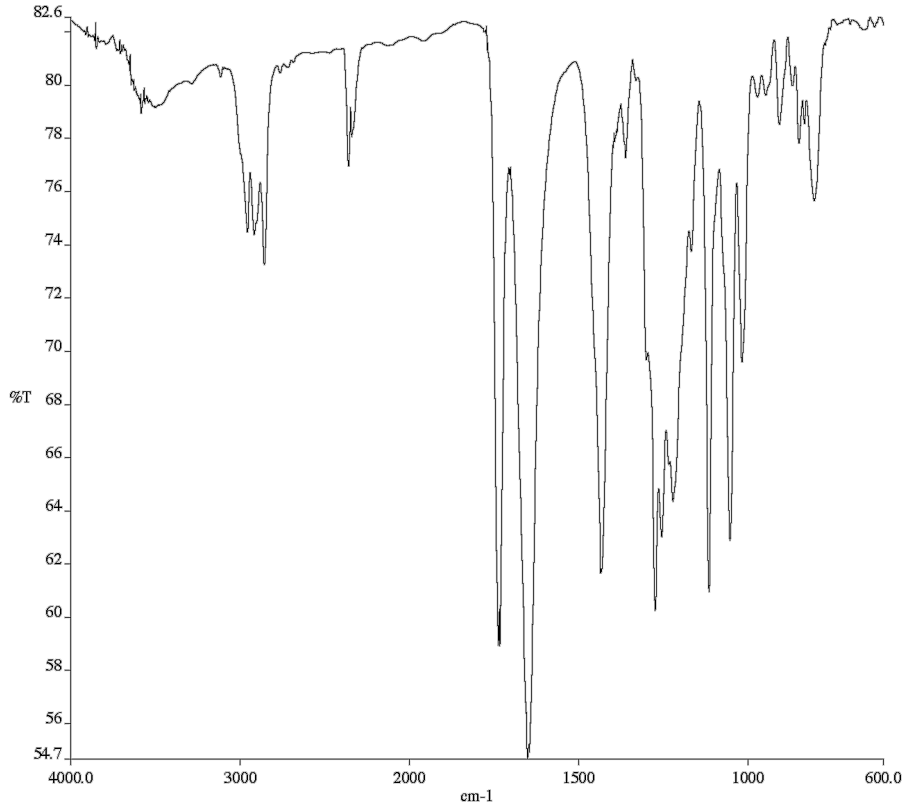


Figure A8.146. Infrared spectrum (Thin Film, NaCl) of compound **175j**

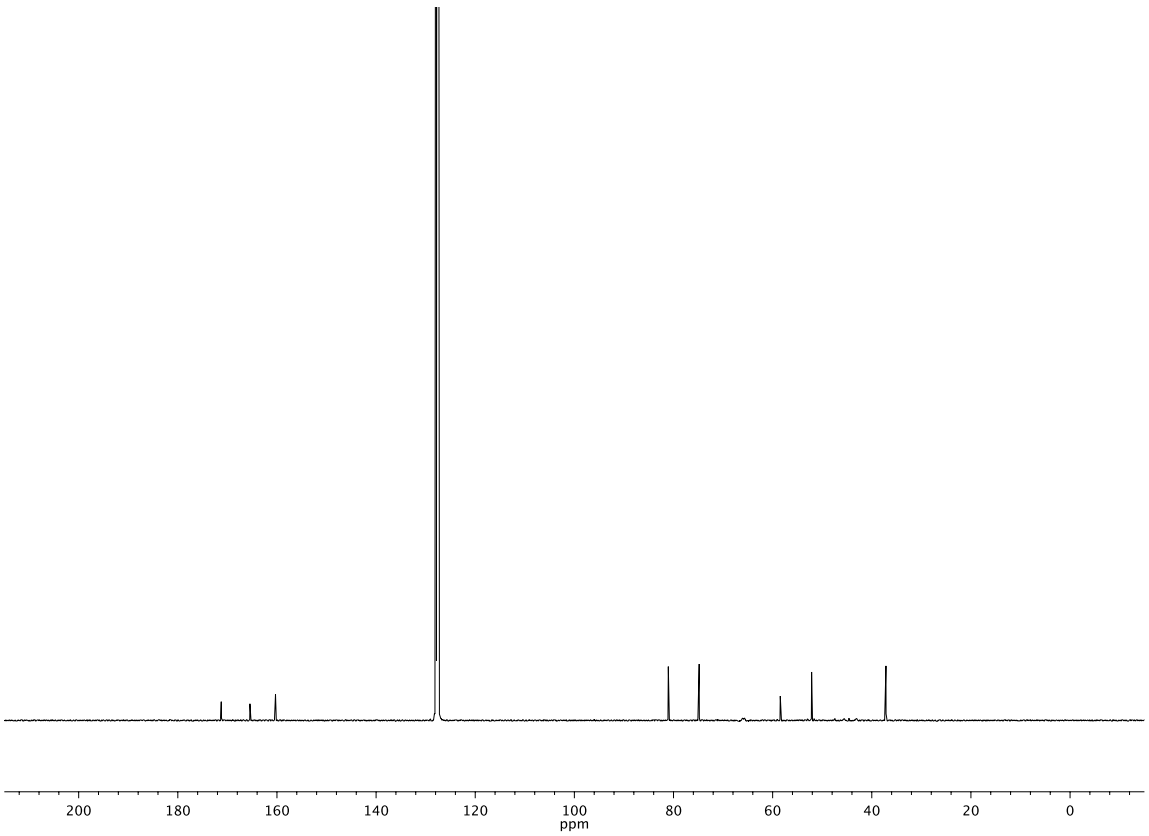


Figure A8.147. ^{13}C NMR (101 MHz, C_6D_6) of compound **175j**.

Figure A8.148. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **174k**.

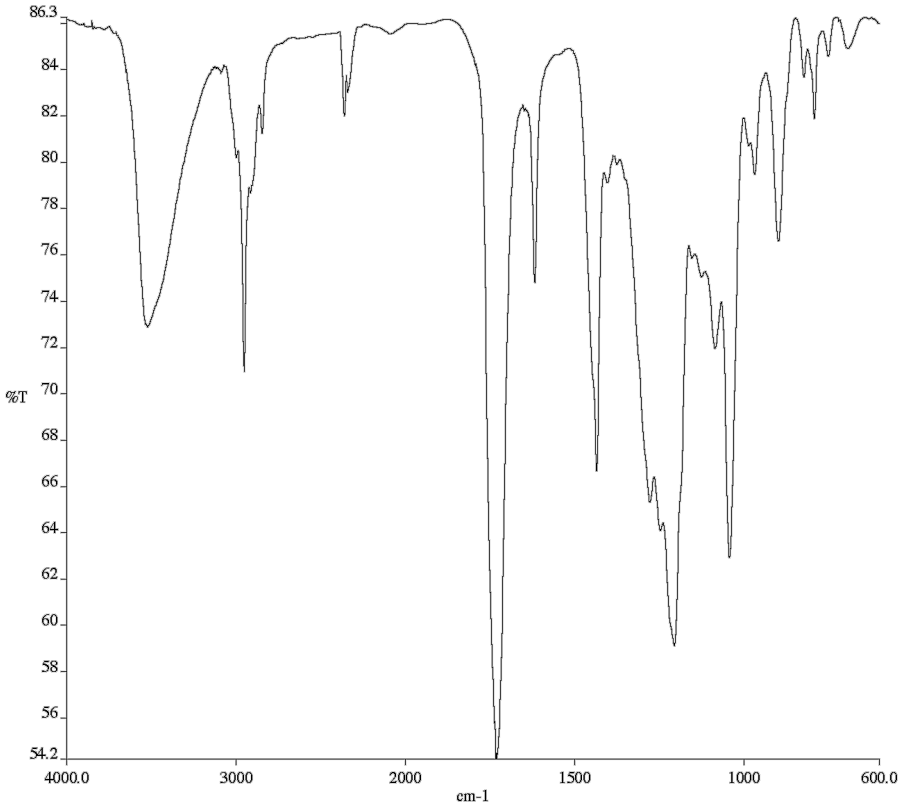


Figure A8.149. Infrared spectrum (Thin Film, NaCl) of compound **174k.**

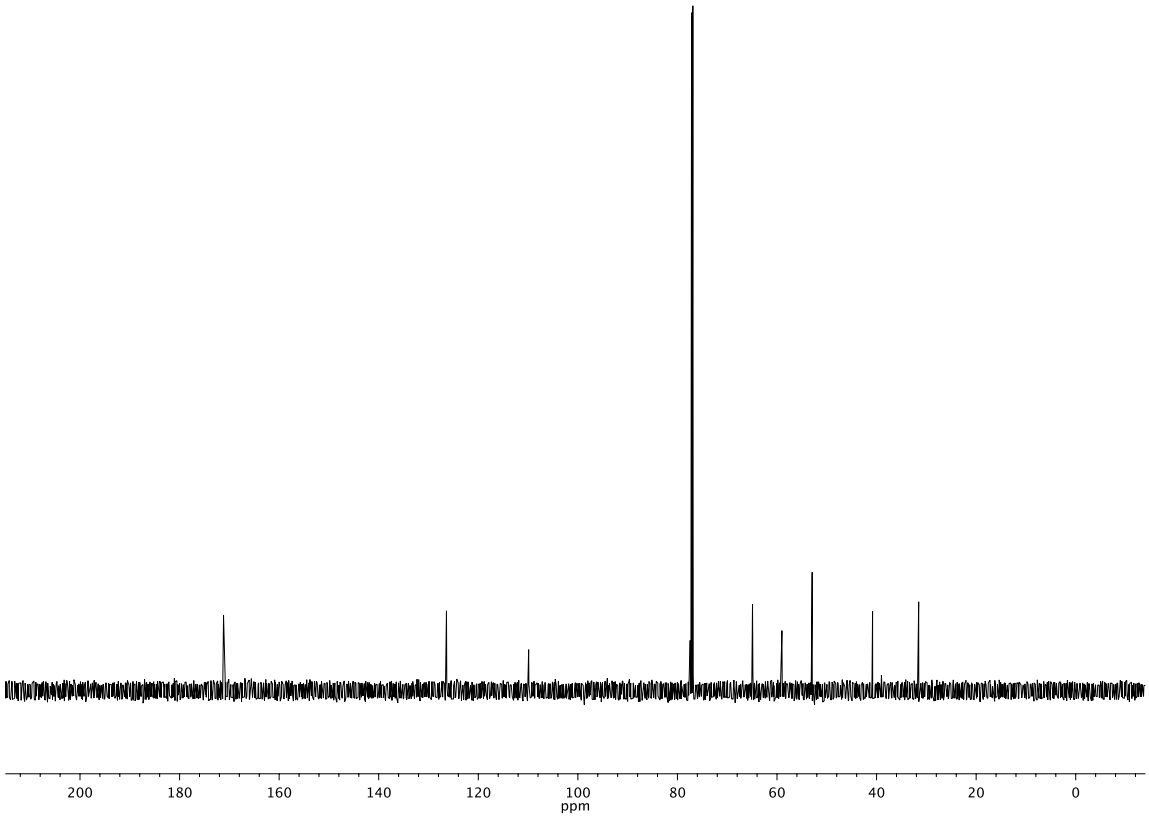
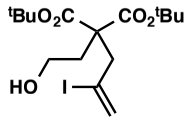


Figure A8.150. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **174k**.



174l

Figure A8.151. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **174l**.

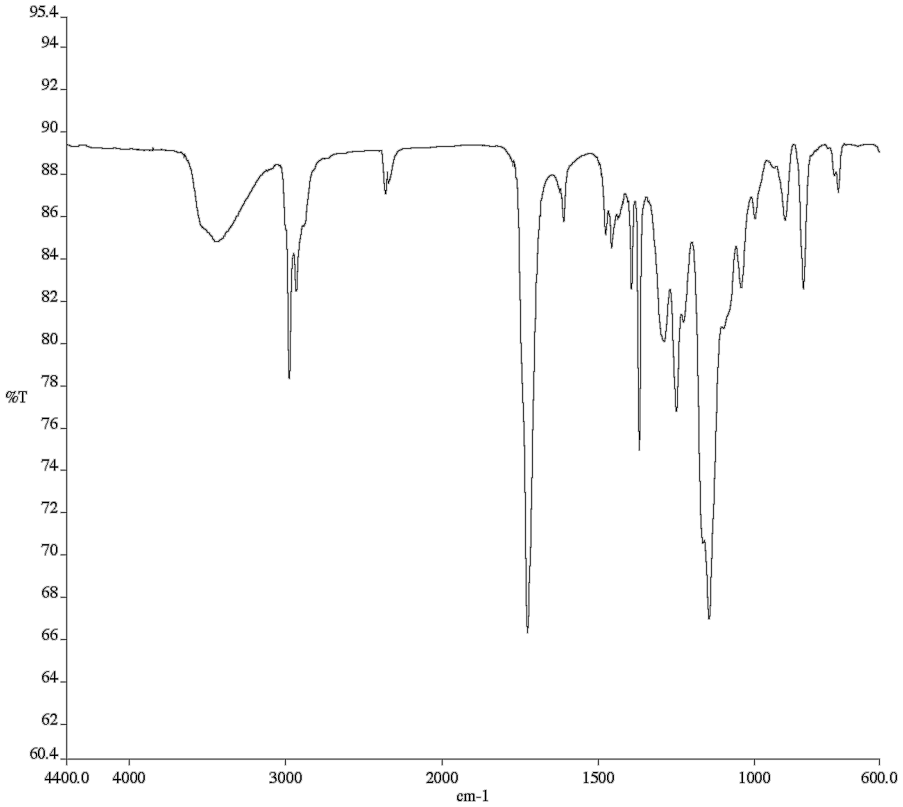


Figure A8.152. Infrared spectrum (Thin Film, NaCl) of compound **174l.**

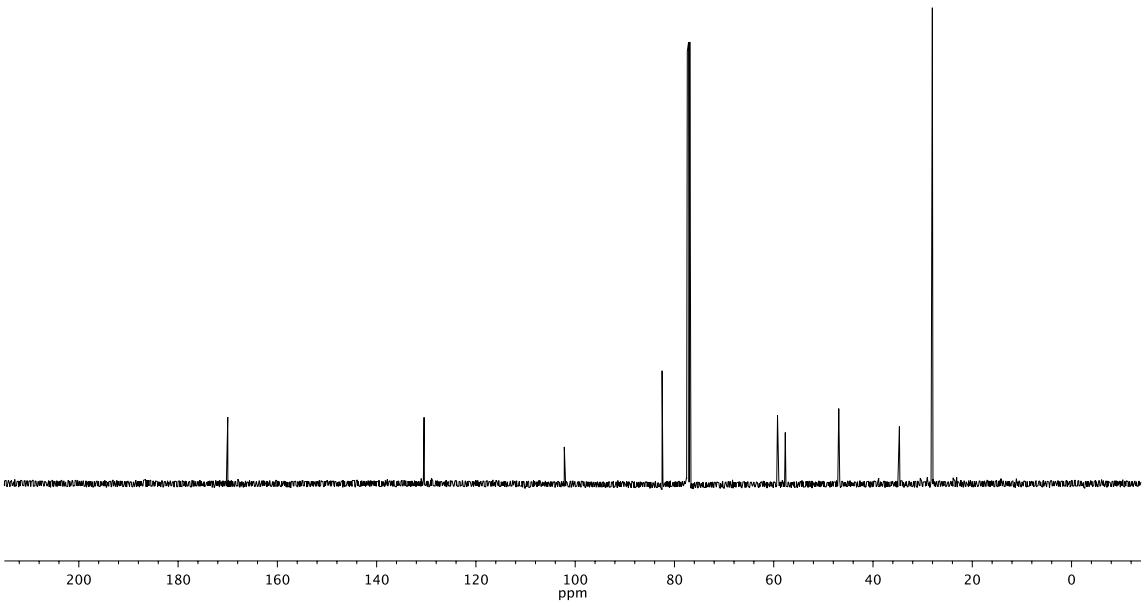


Figure A8.153. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **174l**.

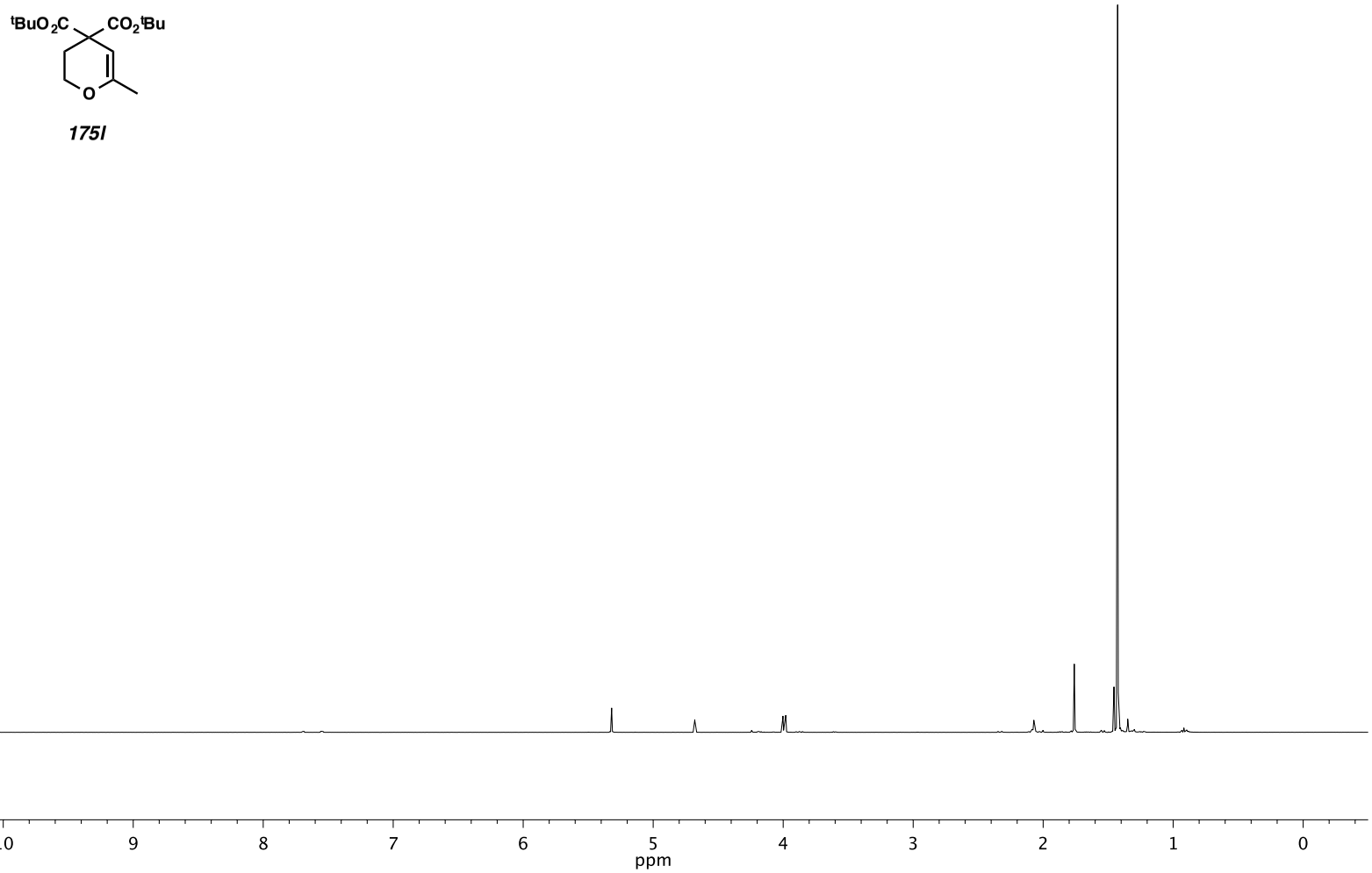


Figure A8.154. ^{1}H NMR (500 MHz, CD_2Cl_2) of compound **175l**.

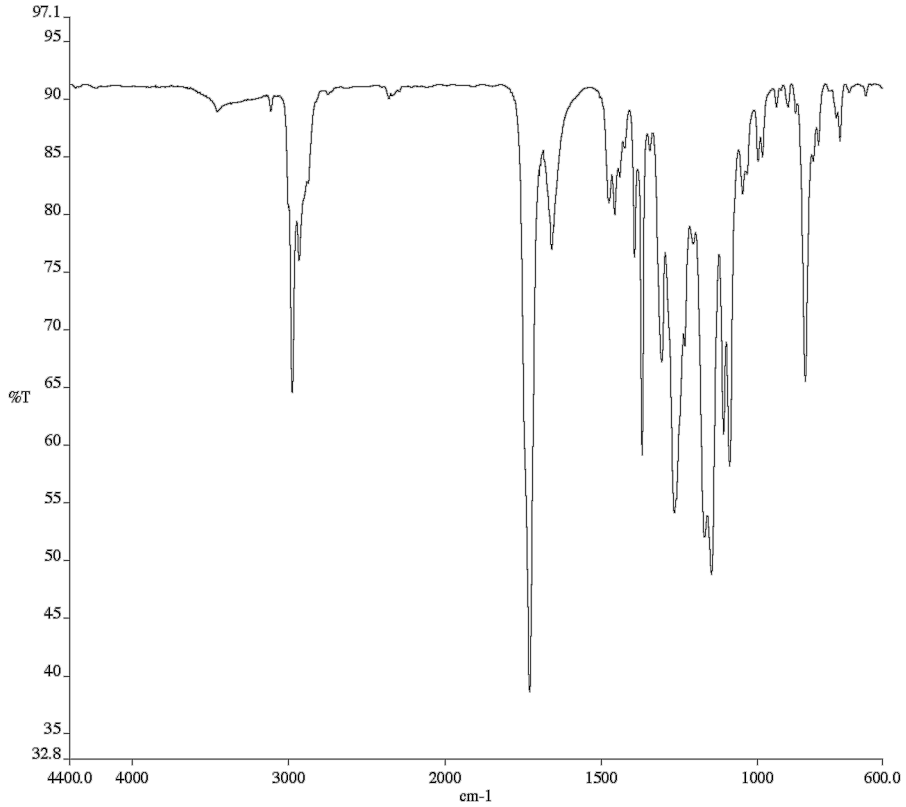


Figure A8.155. Infrared spectrum (Thin Film, NaCl) of compound **175l.**

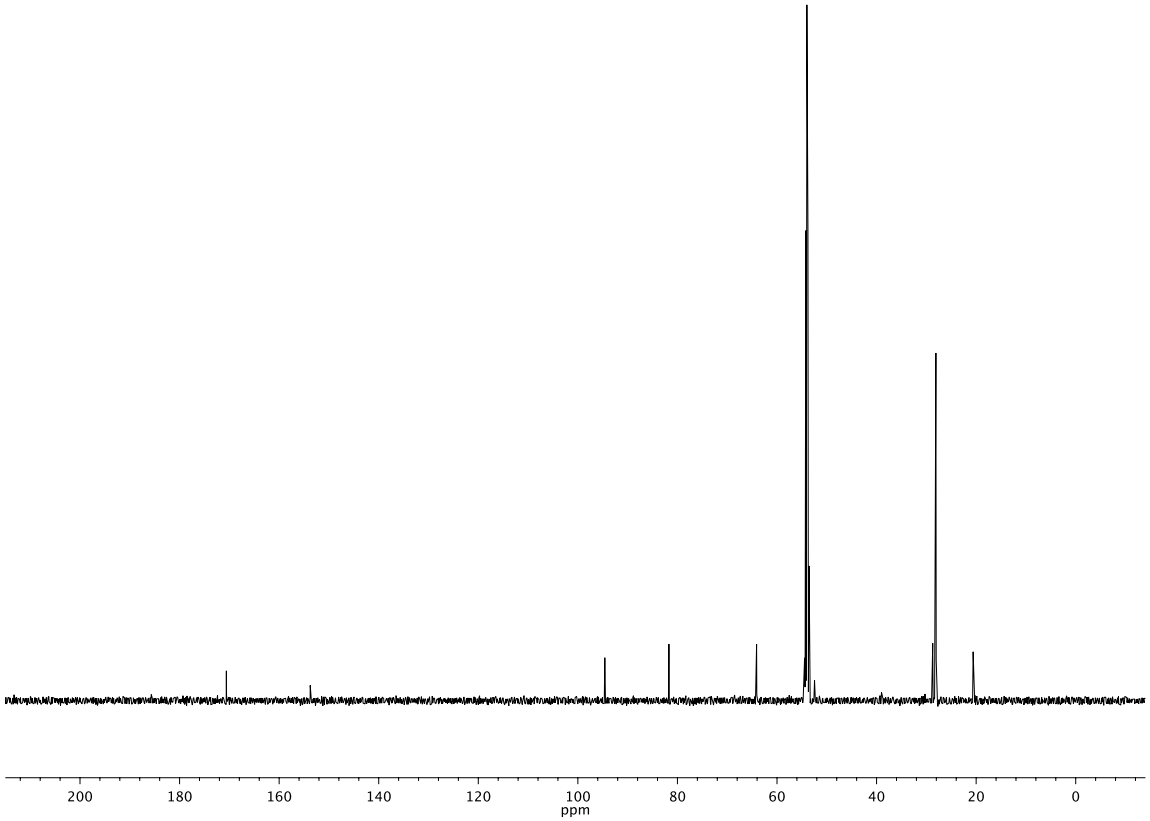


Figure A8.156. ^{13}C NMR (126 MHz, CD_2Cl_2) of compound **175l**.

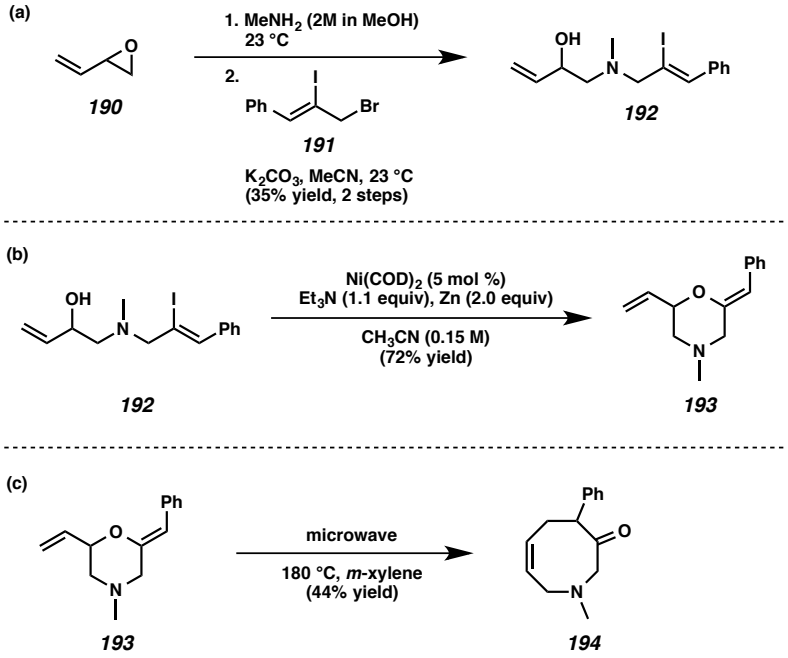
APPENDIX 9

Ni-Catalyzed C–O Bond Formation and Subsequent Claisen Rearrangement

A9.1. Claisen Rearrangement

Having successfully investigated Ni-catalyzed intramolecular C–O bond-forming reactions, we envisaged that allyl vinyl ethers prepared under our conditions could be substrates for subsequent Claisen rearrangement. Treatment of epoxide **190** with methylamine followed by alkylation with allyl bromide **191** afforded aminoalcohol **192** (Scheme A9.1.1a). Intramolecular etherification of aminoalcohol **192** furnished the desired allyl vinyl ether **193** (Scheme A9.1.1b). To our delight, microwave-assisted Claisen rearrangement of vinyl ether **193** in *m*-xylene at 180 °C produced **194** (Scheme A9.1.1c). Further investigation of the substrate scope for Claisen rearrangement is ongoing in our laboratory.

Scheme A9.1.1. *Ni-Catalyzed C–O Bond Formation and subsequent Claisen Rearrangement*



A9.2. Experimental Methods and Analytical Data

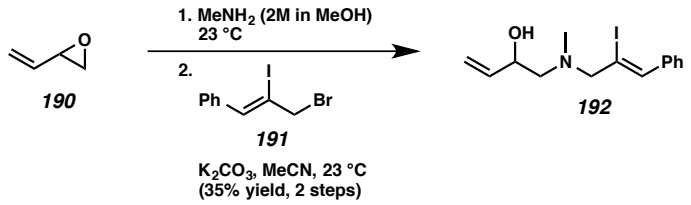
A9.2.1. Materials and Methods

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-MS. THF, Et_2O, CH_2Cl_2, toluene, benzene, CH_3CN, and dioxane were dried by passage through an activated alumina column under argon. Purified water was obtained using a Barnstead NANOpure Infinity UV/UF system. Brine solutions are saturated aqueous solutions of sodium chloride. Commercially available reagents were purchased from Sigma-Aldrich, Acros Organics, TCI, Oakwood chemicals, Strem, or Alfa Aesar and used as received unless otherwise stated. $Ni(COD)_2$ and NiI_2 were purchased from Strem. $NiBr_2$(dme) was purchased from Aldrich. Zinc dust or powder purchased from Aldrich worked well for the reaction but zinc powder (99.999%) purchased from Strem gave poor conversion. Reaction temperatures were

controlled by an IKAmag temperature modulator unless otherwise indicated. Glove box manipulations were performed under a N_2 atmosphere. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, $KMnO_4$ or PMA (phosphomolybdic acid) staining. Silicycle Silia*Flash* P60 Academic Silica gel (particle size 0.040-0.064 mm) was used for flash column chromatography. ^{1}H NMR spectra were recorded on a Varian Mercury 300 MHz, a Bruker AV III HD 400 MHz spectrometer equipped with a Prodigy liquid nitrogen temperature cryoprobe, Varian Inova 500 MHz, and 600 MHz spectrometers and are reported relative to residual $CHCl_3$ (δ 7.26 ppm), $CHDCl_2$ (δ 5.32) or C_6HD_6 (δ 7.16 ppm). ^{13}C NMR spectra are recorded on a Varian Mercury 300 MHz, a Bruker AV III HD 400 MHz spectrometer equipped with a Prodigy liquid nitrogen temperature cryoprobe, Varian Inova 500 MHz, and 600 MHz spectrometers (75 MHz, 126 MHz, and 151 MHz, respectively) and are reported relative to $CHCl_3$ (δ 77.16 ppm), $CHDCl_2$ (δ 53.84) or C_6HD_5 (δ 128.06 ppm). ^{19}F NMR spectra are recorded on a Varian Mercury 300 MHz (at 282 MHz). ^{19}F NMR spectra are reported relative to $CFCl_3$(δ 0.0 ppm). Data for ^{1}H NMR are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d= broad doublet, app = apparent. Data for ^{13}C are reported in terms of chemical shifts (δ ppm). IR spectra were obtained using a Perkin Elmer Paragon 1000 spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using JEOL JMS-600H High Resolution Mass Spectrometer in fast atom bombardment (FAB+) or electron ionization (EI+) mode, or Agilent 6200 Series TOF with an Agilent G1978A

Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed ionization mode (MM: ESI-APCI+).

A9.2.2. Experimental Procedures

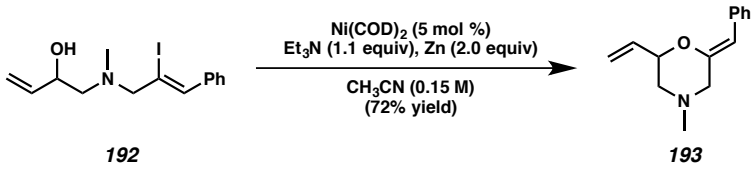


To epoxide **190** (300 mg, 4.28 mmol, 1.00 equiv) was added $MeNH_2$ (2M solution in MeOH; 3.71 mL, 42.8 mmol, 10.0 equiv). The solution was stirred for 12 h at 23 °C. The volatile was evaporated and the residue was used without further purification.

To a solution of the amine (4.28 mmol, 1.00 equiv) in MeCN (11.0 mL) were added K_2CO_3 (2.96 g, 21.4 mmol, 5.00 equiv) and allyl bromide **191** (691 mg, 2.14 mmol, 0.50 equiv). The solution was stirred for 12 h at 23 °C. After the reaction was done, water was added. The aqueous phase was extracted with EtOAc (3 x 7.00 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:4 EtOAc:hexanes) on silica gel to give aminoalcohol **192** (257 mg, 35% yield based on equivalent of allyl bromide **191**, 2 steps).

R_f = 0.65 (1:2 EtOAc:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.55 (m, 2H), 7.43 – 7.34 (m, 3H), 7.10 – 6.98 (s, br, 1H), 5.84 (ddd, *J* = 17.2, 10.5, 5.8 Hz, 1H), 5.45 – 5.37 (m, 1H), 5.21 (dt, *J* = 10.5, 1.5 Hz, 1H), 4.29 (s, br, 1H), 3.54 (s, br, 1H), 3.41 (s, br, 1H), 2.58 (s, br, 2H), 2.40 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.0, 137.2, 136.9, 128.8, 128.4, 128.3, 116.3, 70.7, 68.7, 62.8, 61.1, 41.2; IR (Neat Film

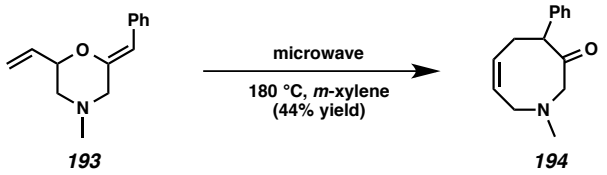
NaCl) 3435, 2795, 1491, 1446, 1083, 1029, 921, 750, 695 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{14}H_{19}NOI$ $[M+H]^+$: 344.0506; found: 344.0523.



192 ***193***

Ni-Catalyzed C–O bond formation experiments were performed in a nitrogen-filled glove box. To a solution of aminoalcohol **192** (100 mg, 0.291 mmol, 1.00 equiv) in MeCN (1.94 mL) in a scintillation vial were added Et_3N (45 μL, 0.320 mmol, 1.10 equiv), Zn powder (38.0 mg, 0.582 mmol, 2.00 equiv), and $Ni(COD)_2$ (4.00 mg, 0.0146 mmol, 0.05 equiv). The reaction mixture was stirred at 23 °C for 24 h. After the reaction was done, the vial was removed from the glovebox and uncapped. Solids were removed via a filtration through a celite plug and the resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) to furnish the product **193** (45.3 mg, 72% yield).

R_f = 0.23 (1:2 EtOAc:hexanes); ^1H NMR (400 MHz, CD_2Cl_2) δ 7.51 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.18 (dd, *J* = 8.4, 7.0 Hz, 2H), 7.08 – 7.01 (m, 1H), 5.89 (ddd, *J* = 17.3, 10.7, 5.6 Hz, 1H), 5.40 – 5.32 (m, 2H), 5.19 – 5.16 (m, 1H), 4.35 (dddt, *J* = 9.8, 5.7, 2.9, 1.5 Hz, 1H), 3.09 (dd, *J* = 12.6, 1.6 Hz, 1H), 2.78 – 2.69 (m, 2H), 2.21 (s, 3H), 2.08 (dd, *J* = 11.7, 9.5 Hz, 1H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 150.5, 136.4, 136.2, 128.9, 128.6, 126.4, 117.1, 107.9, 78.0, 59.5, 58.3, 46.2; IR (Neat Film NaCl) 2939, 2784, 2360, 1666, 1448, 1328, 1239, 1176, 1133, 1047, 985, 937, 755, 694 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{14}H_{18}NO$ $[M+H]^+$: 216.1383; found: 216.1399.



193 *194*

A solution of allyl vinyl ether **193** (11.0 mg, 0.0511 mmol, 1.00 equiv) in *m*-xylene (1.02 mL) was heated to 180 °C (power: 300 W) by microwave for 6 h. The resultant solution was then allowed to cool to ambient temperature, filtered through a pad of SiO_2 using hexanes as the eluent to remove *m*-xylene, at which time separate fractions were collected, eluting with EtOAc, to isolate reaction products. The filtrate was concentrated *in vacuo* and the residue was subsequently purified by flash chromatography (1:2 EtOAc:hexanes) to afford the Claisen product, **194** (4.80 mg, 44% yield).

R_f = 0.39 (1:2 EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.41 (m, 2H), 7.35 (ddd, *J* = 7.7, 6.8, 1.2 Hz, 2H), 7.30 – 7.27 (m, 1H), 5.94 (m, 1H), 5.61 (dt, *J* = 10.8, 5.1 Hz, 1H), 3.87 (d, *J* = 13.9 Hz, 2H), 3.55 (d, *J* = 15.7 Hz, 1H), 3.42 (d, *J* = 15.3 Hz, 1H), 3.04 (t, *J* = 15.5 Hz, 1H), 2.84 (d, *J* = 15.4 Hz, 1H), 2.47 – 2.42 (m, 1H), 2.40 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.7, 138.3, 130.9, 129.0, 128.7, 128.1, 127.6, 66.1, 61.3, 58.1, 45.9, 29.1; IR (Neat Film NaCl) 2928, 2791, 1696, 1493, 1451, 1268, 1126, 699 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{14}H_{18}NO$ $[M+H]^+$: 216.1383; found: 216.1398.

APPENDIX 10

Spectra Relevant to Appendix 9:

Ni-Catalyzed C–O Bond Formation and Subsequent Claisen Rearrangement

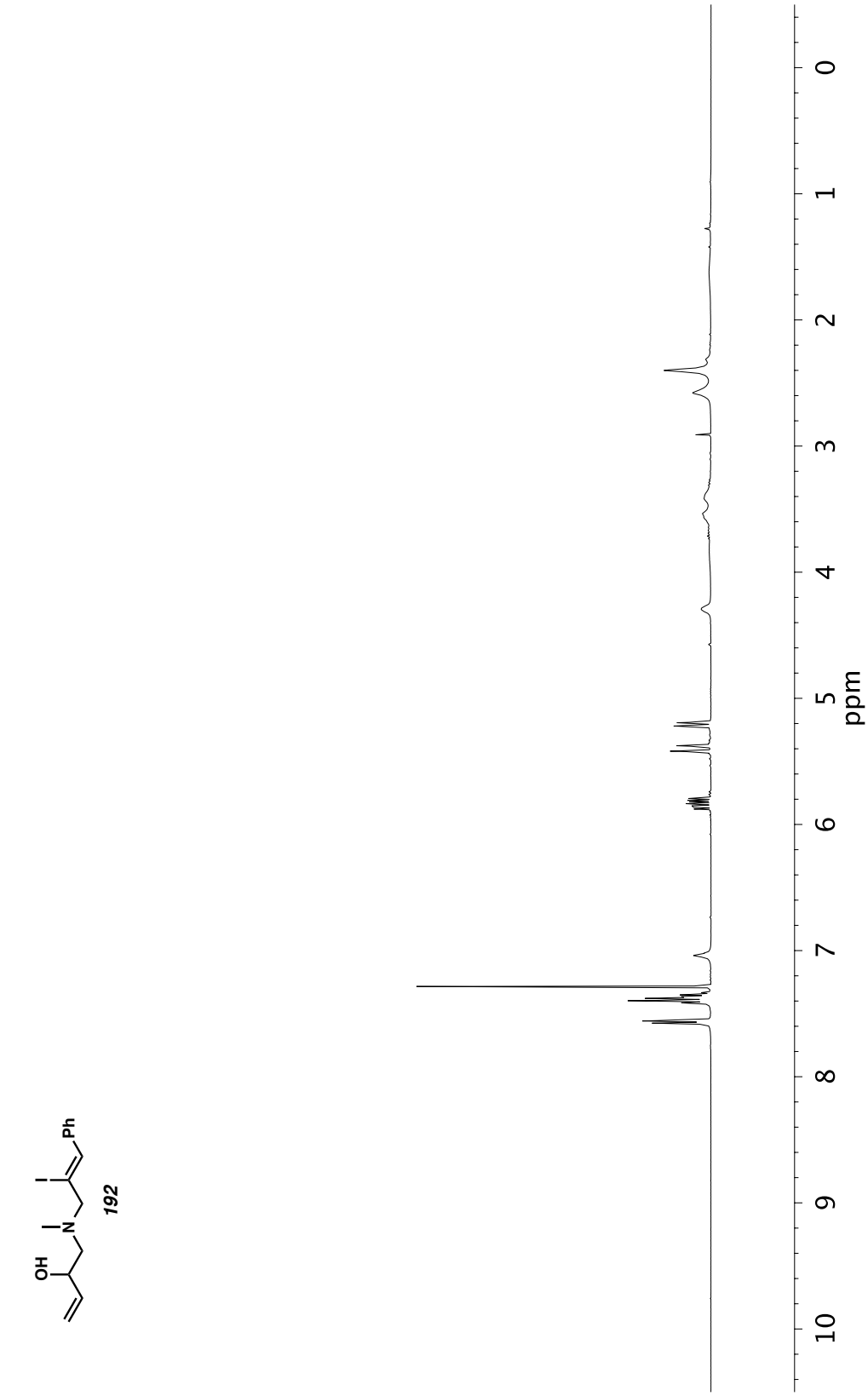


Figure A10.1. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **192**.

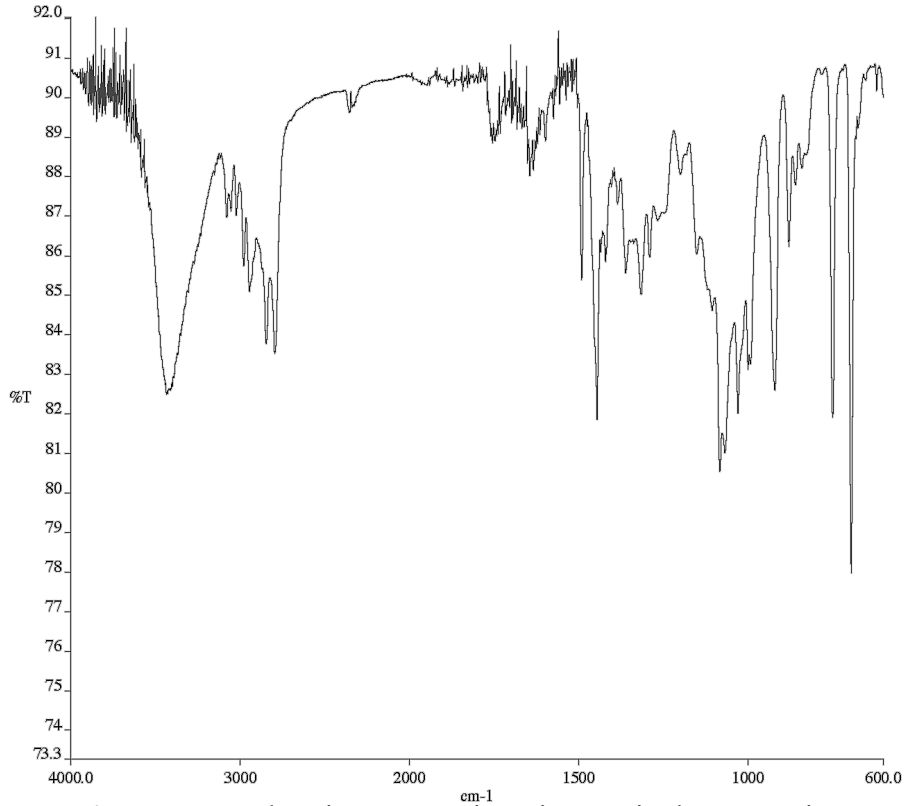


Figure A10.2. Infrared spectrum (Thin Film, NaCl) of compound **192**.

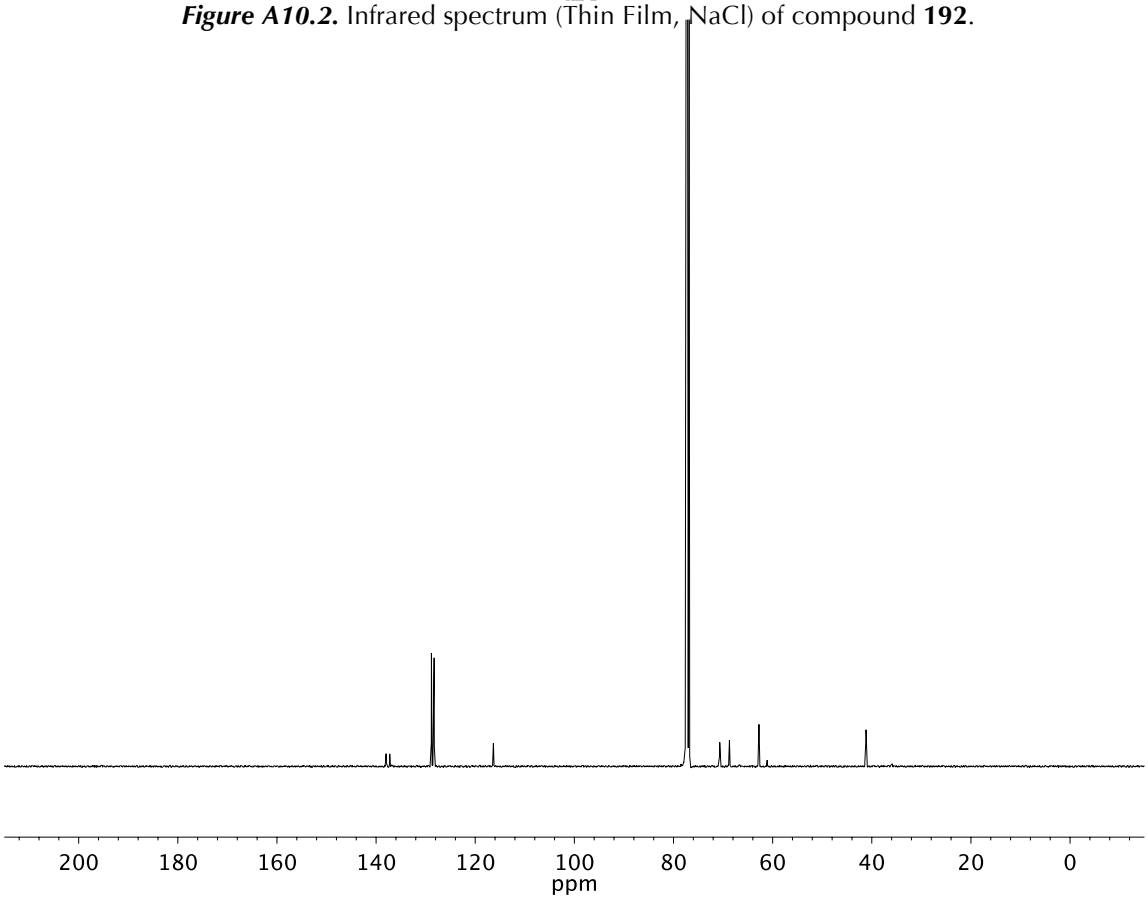


Figure A10.3. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **192**.

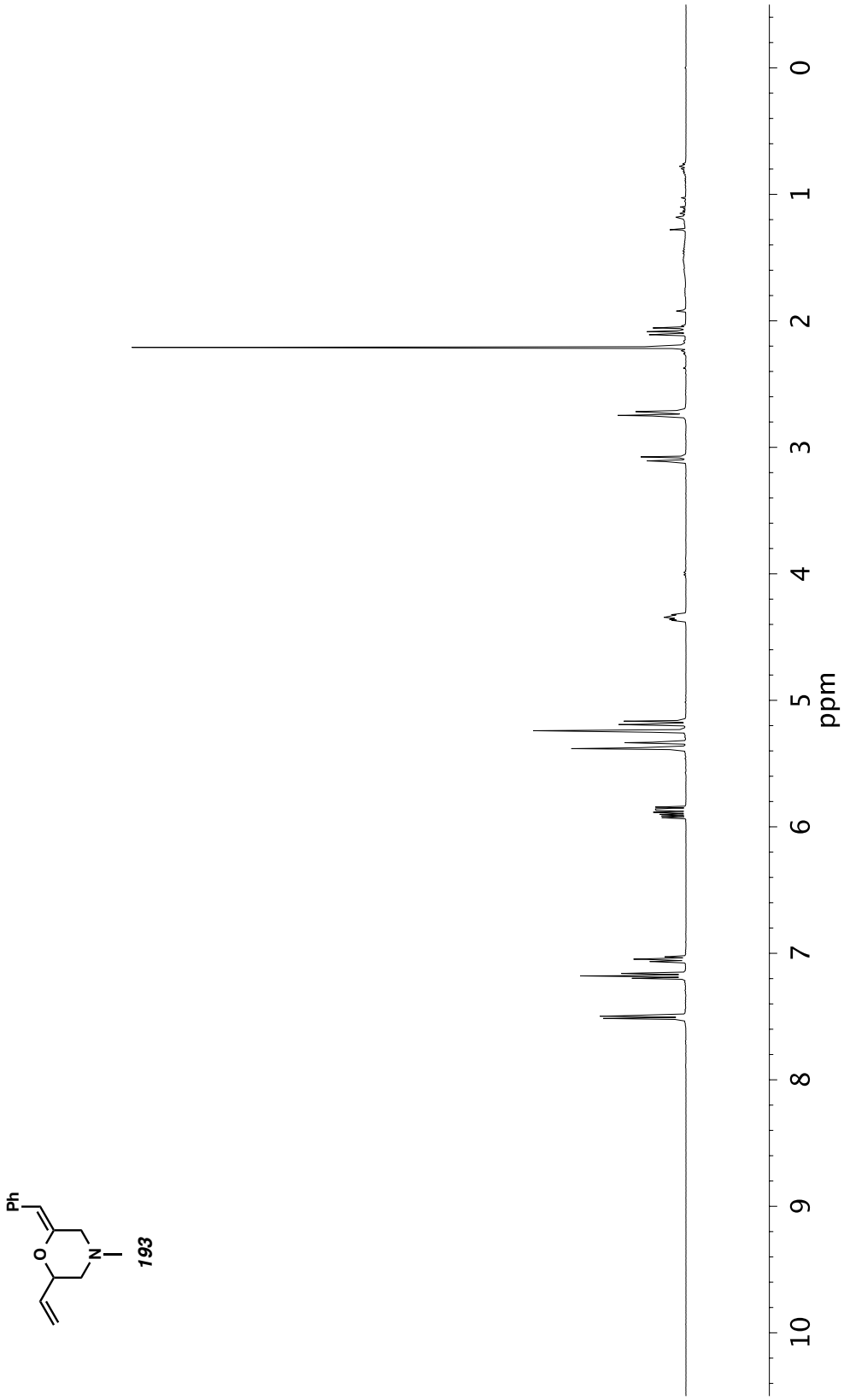


Figure A10.4. ^{1}H NMR (400 MHz, CD_2Cl_2) of compound **193**.

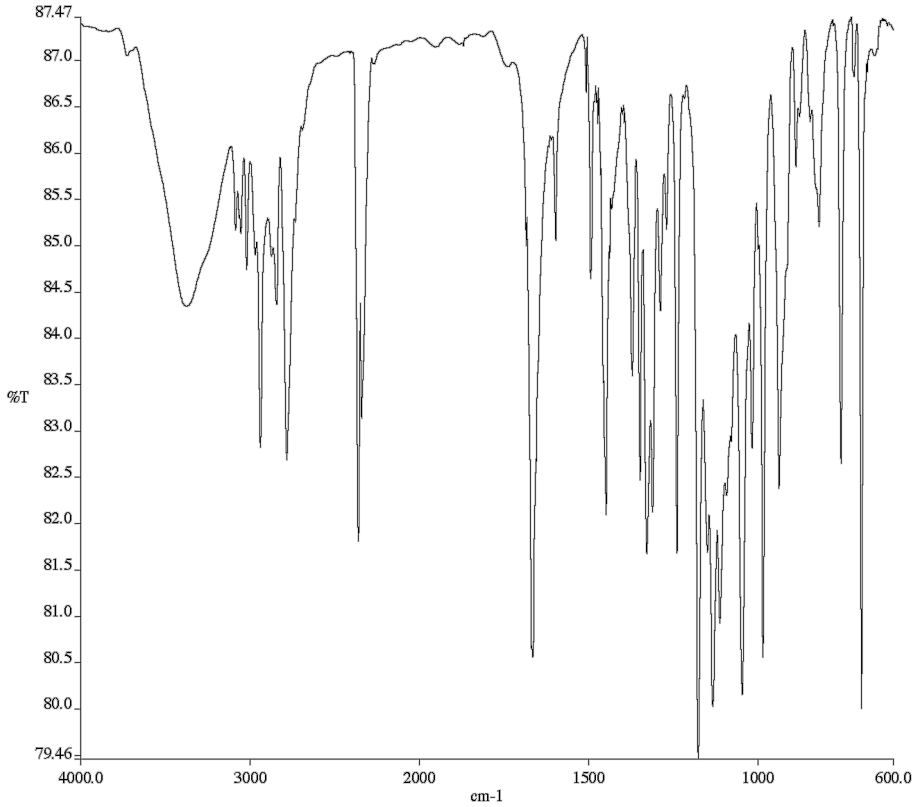


Figure A10.5. Infrared spectrum (Thin Film, NaCl) of compound **193**.

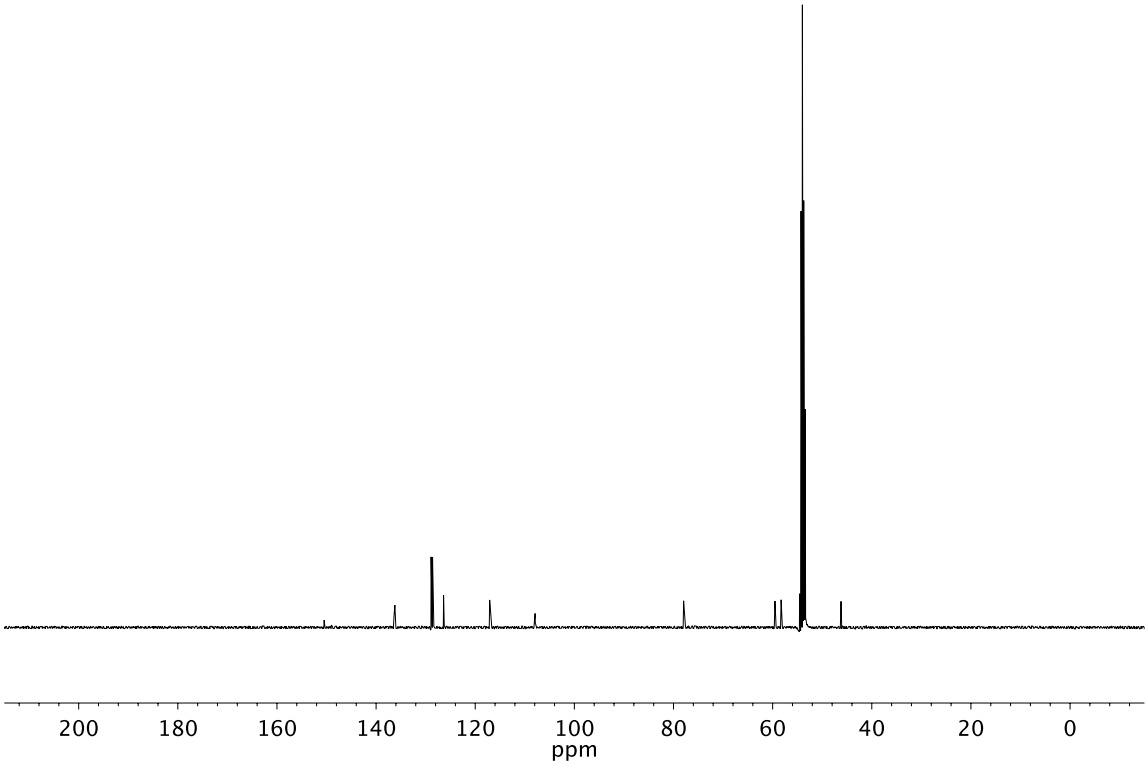


Figure A10.6. ^{13}C NMR (101 MHz, CD_2Cl_2) of compound **193**.

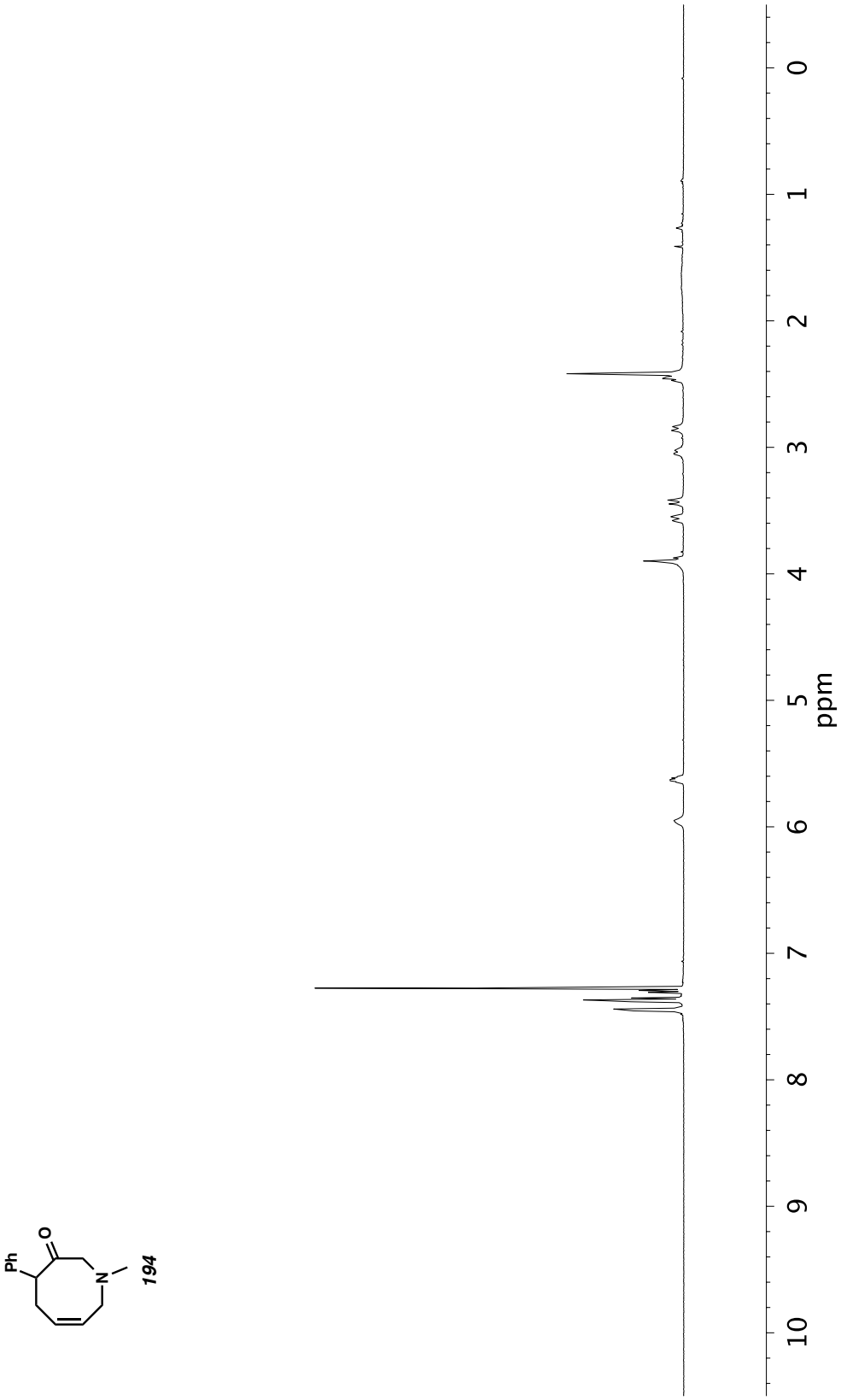


Figure A10.7. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **194**.

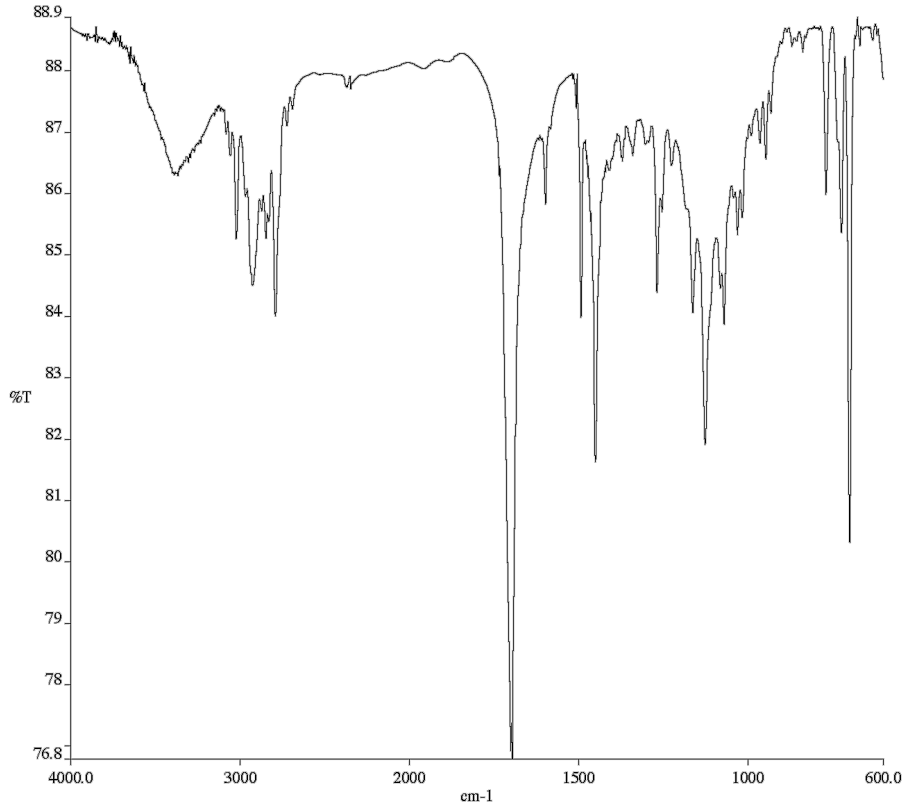


Figure A10.8. Infrared spectrum (Thin Film, NaCl) of compound **194**.

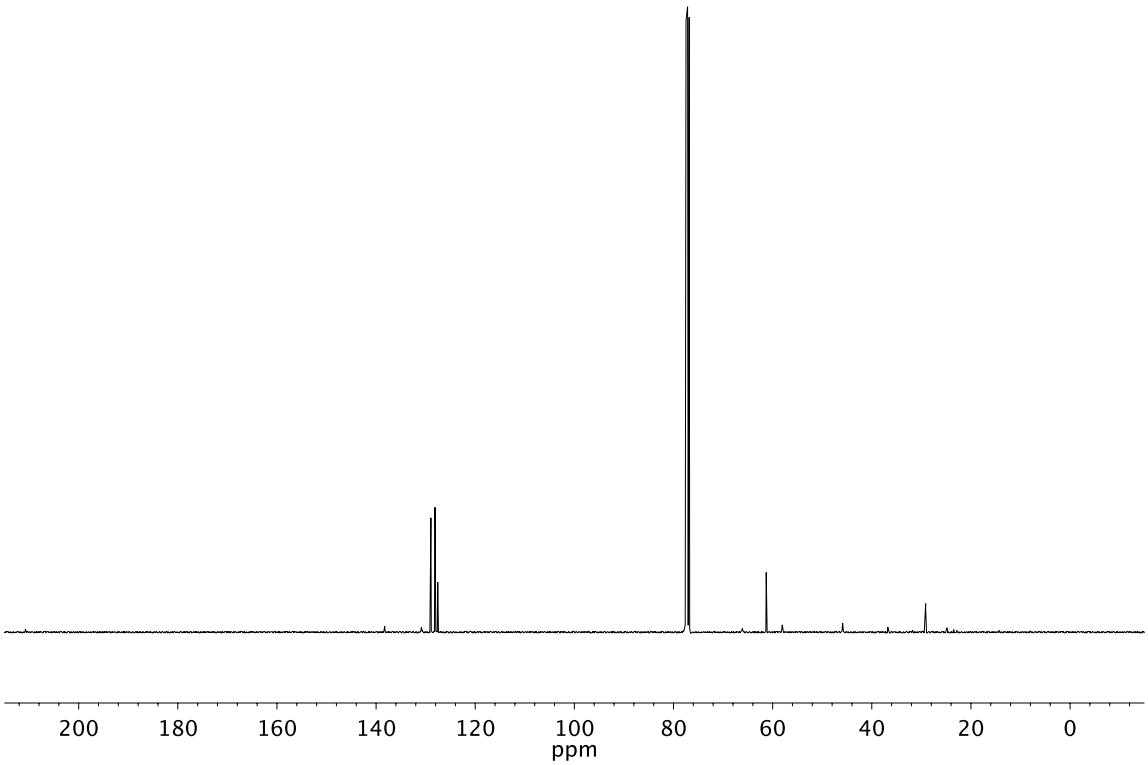


Figure A10.9. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **194**.

APPENDIX 11

Synthetic Studies Toward Alistonitrine A[†]

A11.1. Introduction

The polycyclic monoterpene alkaloid alistonitrine A (**195**) was isolated from the leaves of *Alstonia scholaris* in 2014 by the Bai and Jiang groups (Figure A11.1.1).[1] The alkaloids extracted from *Alstonia scholaris* possess interesting biological properties such as anticancer, antibacterial, anti-inflammatory, antiasthmatic, expectorant, analgesic, and antitussive activities.[2] Alistonitrine A (**195**) possesses intriguing structural features including an unprecedented caged skeleton, consecutive aminals, an epoxide, and a polycyclic system. Synthetic studies toward alistonitrine A have not been reported to date. Herein, we describe our synthetic efforts toward alistonitrine A (**195**).

Figure A11.1.1. *Structure of Alistonitrine A (**195**)*

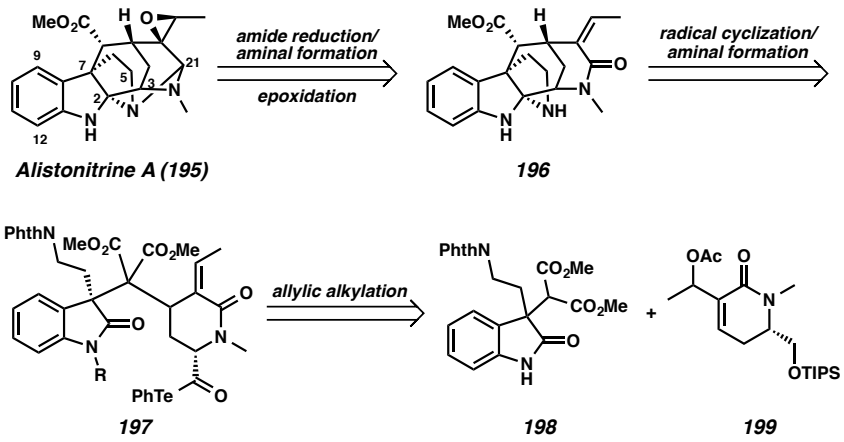
Alistonitrine A (195)

[†] Portions of this work have been published. Han, S.-J.; Stoltz, B. M. *Tetrahedron Lett*. **2016**, DOI: 10.1016/j.tetlet.2016.04.022

A11.2. Results and Discussion

Our initial retrosynthetic analysis of alistonitrine A is outlined in Scheme A11.2.1. Disconnection of the aminal at the C21 and epoxide functions in alistonitrine A (**195**) would afford amide **196**. Further cleavage of the C2–C3 bond and the second aminal functional group would provide intermediate **197**, in which the acyl telluride would serve as a handle for a decarbonylative radical cyclization.[3] We envisioned that the vicinal quaternary centers of intermediate **197** could be constructed by coupling of oxindole **198** and amide **199**.

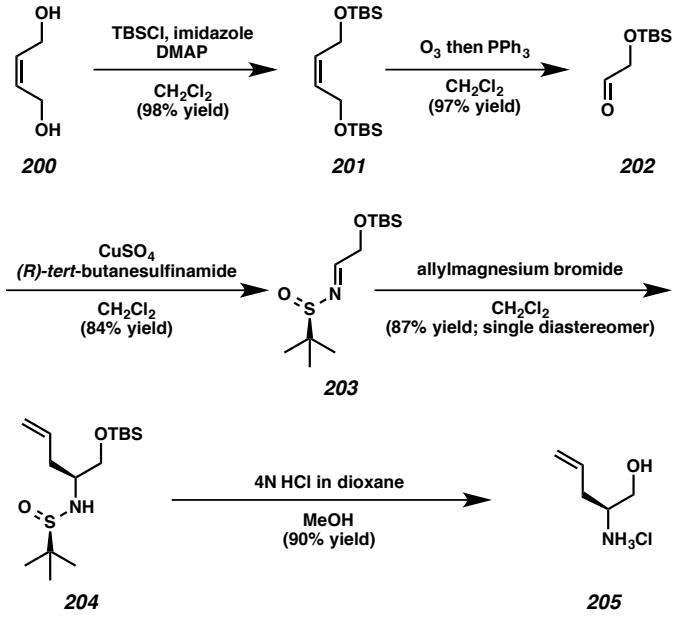
Scheme A11.2.1. *Retrosynthetic Analysis of Alistonitrine A (**195**)*



The synthesis commenced with the construction of amine **205**, which was adapted from Ellman and Nelson protocols (Scheme A11.2.2). Protection of diol **200** with TBSCl furnished bis-silyl ether **201**, which was converted to aldehyde **202** by ozonolysis. Condensation with (*R*)-*tert*-butanesulfinamide auxiliary produced *tert*-butylsulfinyl imine **203**.[4,5] 1,2-addition of allylmagnesium bromide to *tert*-butylsulfinyl imine **203** generated

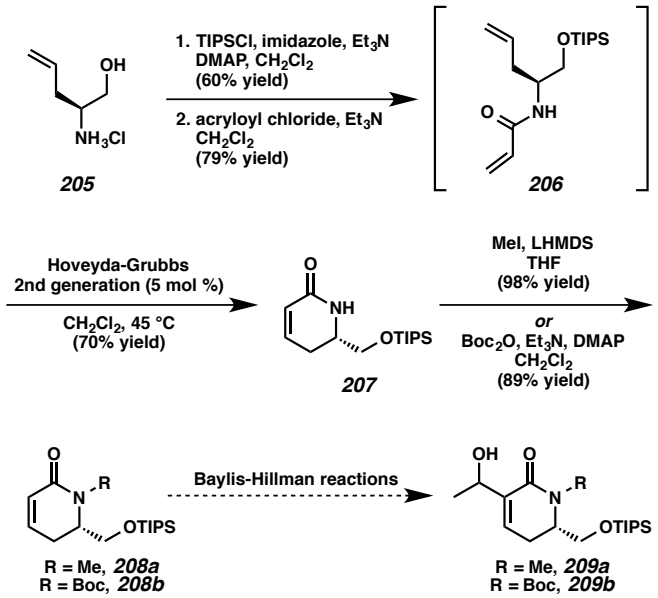
adduct **204** in high diastereoselectivity. Cleavage of the silyl and *tert*-butanesulfinyl groups under acidic conditions afforded chiral amine **205**.

Scheme A11.2.2. *Synthesis of Chiral Amine* ***205***



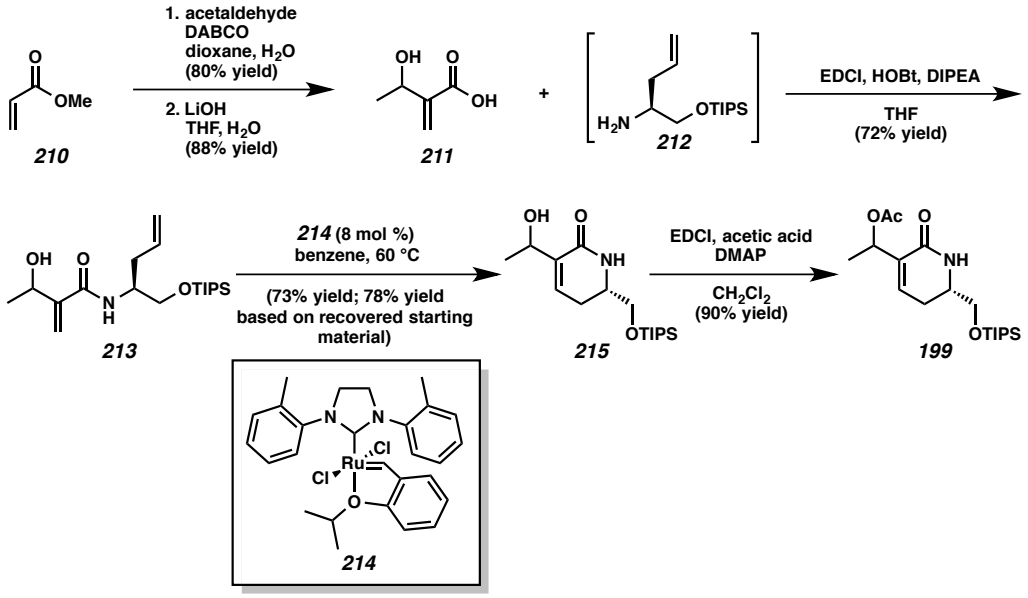
With chiral amine **205** in hand, α,β-unsaturated lactam formation was explored (Scheme A11.2.3). Silylation of amine **205** followed by acylation generated metathesis precursor **206**. We were delighted to find that ring-closing metathesis of **206** with Hoveyda-Grubbs 2nd generation catalyst smoothly produced lactam **207**.[6,7] Protection of the nitrogen of amide **207** with MeI or Boc_2O afforded the corresponding intermediates **208a** and **208b**. Unfortunately, attempted Baylis-Hillman reactions to furnish alcohol **209a** or **209b**, respectively, were unsuccessful.[8,9]

Scheme A11.2.3. *Synthesis of α,β-Unsaturated Lactams* ***208***



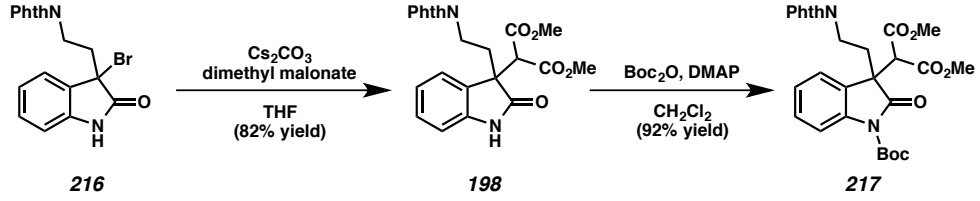
Alternatively, we decided to employ the Baylis-Hillman reaction at an earlier stage (Scheme A11.2.4). Reaction of methyl acrylate (**210**) with acetaldehyde and subsequent hydrolysis furnished acid **211**. Coupling of acid **211** and amine **212** with EDCI and HOBt proceeded smoothly to provide amide **213**. To our delight, ring-closing metathesis of **213** occurred with catalyst **214**, delivering the desired 2:3 mixture of two diastereomers of lactam **215**.[10] Coupling of alcohol **215** and acetic acid with EDCI and HOBt generated acetate **199**.

Scheme A11.2.4. *Synthesis of α,β-Unsaturated Lactam* ***199***



Having successfully prepared the amide fragment, we began the synthesis of the oxindole fragment **217** (Scheme A11.2.5). The quaternary center of oxindole **198** was constructed by the base-promoted alkylation of 3-bromooxindole **216** with dimethyl malonate, which proceeded via *in situ* formation of an *o*-azaxylylene intermediate.[11] Boc protection of the oxindole nitrogen generated oxindole fragment **217**.

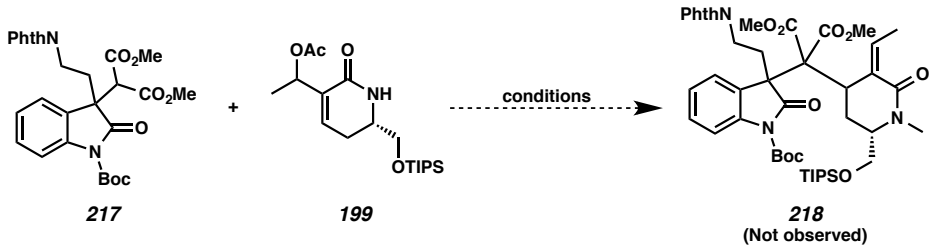
Scheme A11.2.5. *Synthesis of Oxindole Fragment* ***217***



With fragments **199** and **217** in hand, we investigated various alkylation reactions of malonate **217** with acetate **199** (Scheme A11.2.6). Unfortunately, only trace amounts

of the desired product and some byproducts were observed with palladium catalysts. Additionally, we attempted to form **218** under basic conditions, but only unreacted oxindole **217** and a byproduct were obtained.

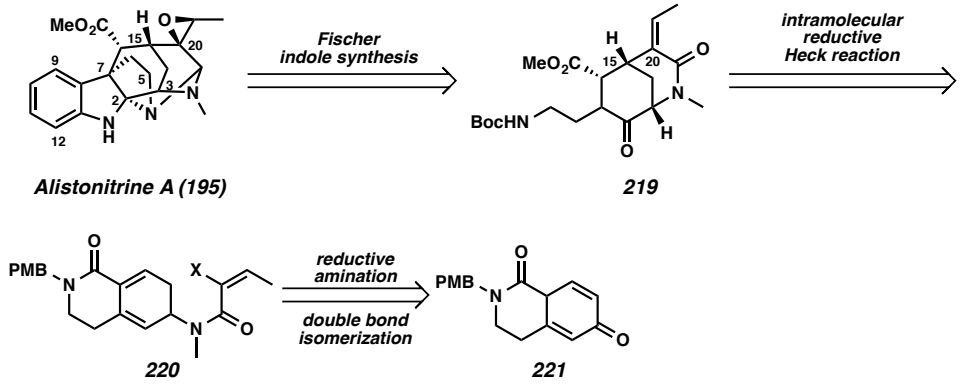
Scheme A11.2.6. *Attempted Coupling of Malonate **217** and Amide **199***



217 ***199*** ***218*** **(Not observed)**

Having failed in coupling of oxindole **217** and amide **199**, a revised retrosynthesis was devised (Scheme A11.2.7). We envisioned that a late stage Fischer indole synthesis of intermediate **219** would afford the core structure of alistonitrine A. Disconnection of the C15–C20 bond in intermediate **219** provided Heck reaction precursor **220**. Vinyl halide **220** was expected to be formed from ketone **221** by reductive amination and subsequent double bond isomerization.

Scheme A11.2.7. *A Revised Retrosynthesis Toward Alistonitrine A*

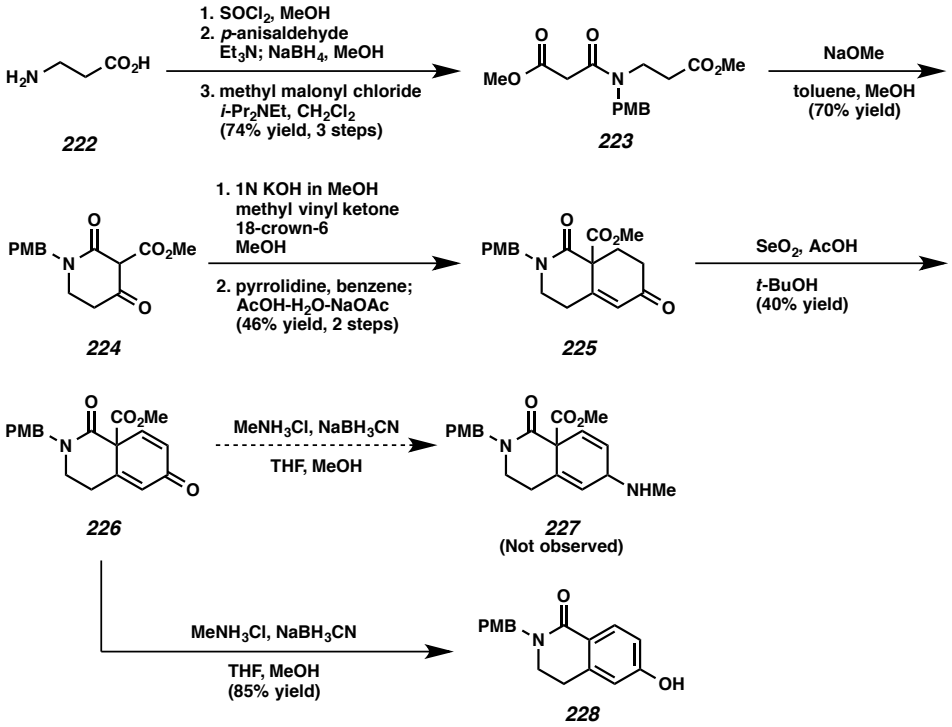


Alistonitrine A (195) ***219*** ***220*** ***221***

Esterification of acid **222** followed by subsequent reductive amination and acylation produced amide **223** (Scheme A11.2.8). Treatment of **223** with NaOMe afforded lactam **224**, and a subsequent Robinson annulation furnished bicycle **225**.[12] Oxidation of enone **225** was accomplished with SeO_2 to deliver dienone **226**.[13] However, an attempted reductive amination of dienone **226** to provide amine **227** resulted in the removal of the ester group and subsequent aromatization, affording phenol **228**.

Although our synthetic efforts toward alistonitrine A were unsuccessful, we were able to serendipitously discover a novel nickel-catalyzed C–O bond forming reaction (Chapter 4).

Scheme A11.2.8. *Synthesis of Bicycle* ***226***



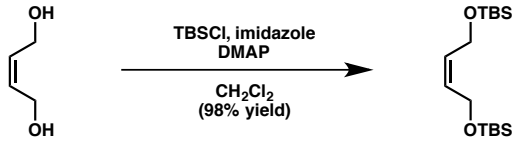
A11.3. Experimental Methods and Analytical Data

A11.3.1. Materials and Methods

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Reaction progress was monitored by thin-layer chromatography (TLC). THF, Et_2O, CH_2Cl_2, toluene, benzene, CH_3CN, and dioxane were dried by passage through an activated alumina column under argon. Triethylamine was distilled over CaH_2 prior to use. Purified water was obtained using a Barnstead NANOpure Infinity UV/UF system. Brine solutions are saturated aqueous solutions of sodium chloride. Commercially available reagents were purchased from Sigma-Aldrich, Acros Organics, Strem, or Alfa Aesar and used as received unless otherwise stated. Reaction temperatures were controlled by an IKAmag temperature modulator unless otherwise indicated. Microwave-assisted reactions were performed in a Biotage Initiator 2.5 microwave reactor. Glove box manipulations were performed under a N_2 atmosphere. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, or PMA (phosphomolybdic acid) staining. Silicycle Silia*Flash* P60 Academic Silica gel (particle size 0.040-0.064 mm) was used for flash column chromatography. ^{1}H NMR spectra were recorded on a Varian Inova 500 MHz spectrometer and are reported relative to residual $CHCl_3$ (δ 7.26 ppm), or $(CD_3)_2CO$ (δ 2.05 ppm). ^{13}C NMR spectra are recorded on a Varian Inova 500 MHz spectrometer (125MHz) and are reported relative to $CHCl_3$ (δ 77.16 ppm), or $(CD_3)_2CO$ (δ 29.84 ppm). Data for ^{1}H NMR are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d= broad doublet, app

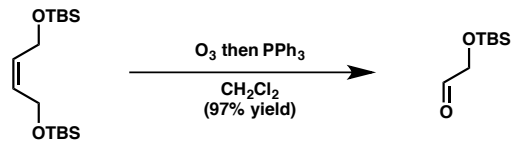
= apparent. Data for ^{13}C are reported in terms of chemical shifts (ppm). IR spectra were obtained using a Perkin Elmer Paragon 1000 spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). High resolution mass spectra (HRMS) were obtained from Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed ionization mode (MM: ESI-APCI+).

A11.3.2. Experimental Procedures



200 ***201***

To a solution of diol **200** (0.930 mL, 11.3 mmol, 1.00 equiv) in CH_2Cl_2 (28.3 mL) were added imidazole (7.69 g, 113 mmol, 10.0 equiv) and TBSCl (5.11 g, 33.9 mmol, 3.00 equiv) at 23 °C. The reaction mixture was stirred for 12 h and quenched with water. The aqueous phase was extracted with CH_2Cl_2 (3 x 10.0 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (1:8 EtOAc:hexanes) to afford bis-silyl ether **201** (3.51 g, 98% yield). The spectroscopic data were identical to those previously reported.[1]

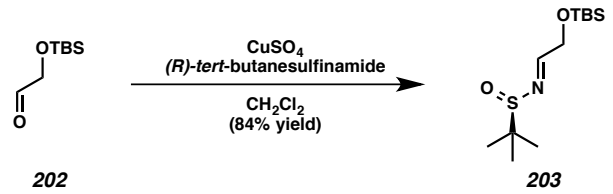


201 ***202***

[1] Tran, V. T.; Woerpel, K. A. *J. Org. Chem.* **2013**, *78*, 6609–6621.

A solution of bis-silyl ether **201** (1.00 g, 3.16 mmol, 1.00 equiv) in CH_2Cl_2 (21.1 mL) was cooled to –78 °C and ozone was bubbled through until the solution turned blue. N_2 gas was then bubbled through the solution until the reaction mixture turned colorless. PPh_3 (0.99 g, 3.79 mmol, 1.20 equiv) was then added and the mixture was warmed to 23 °C slowly. The reaction mixture was stirred under N_2 for 1.5 h and the solvent was evaporated *in vacuo*. The residue was purified by silica gel chromatography (1:8 EtOAc:hexanes) to afford aldehyde **202** (1.07 g, 97% yield).

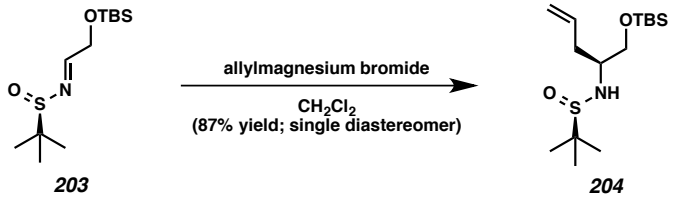
R_f = 0.25 (1:8 EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.70 (t, J = 0.8 Hz, 1H), 4.22 (d, J = 0.8 Hz, 2H), 0.93 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.5, 69.8, 25.9, 18.5, -5.3; IR (Neat Film NaCl) 2955, 2931, 2858, 1740, 1473, 1256, 1128, 838, 779 cm^{-1}; HRMS (MM: FAB+) *m/z* calc'd for $C_8H_{19}O_2Si$ $[M+H]^+$: 175.1154; found: 175.1067.



202 *203*

To a solution of aldehyde **202** (100 mg, 0.574 mmol, 1.00 equiv) in CH_2Cl_2 (1.91 mL) was added $CuSO_4$ (275 mg, 1.72 mmol, 3.00 equiv) followed by the addition of *tert*-butanesulfinamide (104 mg, 0.861 mmol, 1.50 equiv). The reaction mixture was stirred at 23 °C for 12 h. Solids were removed via a filtration through a celite plug and the resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography (1:8 EtOAc:hexanes) to furnish the *tert*-butylsulfinyl imine **203** (133 mg, 84% yield).

$[a]_D^{25}$ –127.8 (*c* 0.19, $CHCl_3$); R_f = 0.20 (1:8 EtOAc:hexanes); ^1H NMR (400 MHz, CD_2Cl_2) δ 7.99 (t, J = 3.1 Hz, 1H), 4.53 (d, J = 3.1 Hz, 2H), 1.17 (s, 9H), 0.92 (s, 9H), 0.10 (d, J = 0.6 Hz, 6H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 169.1, 66.1, 57.1, 26.1, 22.6, 18.8, -5.1; IR (Neat Film NaCl) 2956, 2930, 2858, 1628, 1473, 1364, 1255, 1089, 838, 779 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{12}H_{28}NO_2SSi$ $[M+H]^+$: 278.1605; found: 278.1606.

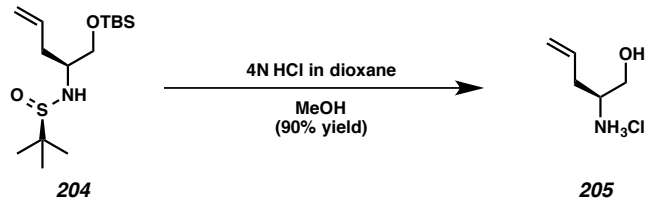


203 ***204***

To a solution of *tert*-butylsulfinyl imine **203** (800 mg, 2.88 mmol, 1.00 equiv) in CH_2Cl_2 (14.4 mL) was added allylmagnesium bromide (1M in diethyl ether; 6.05 mL, 6.05 mmol, 2.10 equiv) dropwise at –78 °C. The reaction mixture was stirred for 5 h at –78 °C and slowly warmed to 23 °C. The reaction was quenched with sat. aq NH_4Cl. The aqueous phase was extracted with CH_2Cl_2 (3 x 10.0 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (1:4 EtOAc:hexanes) to afford silyl ether **204** (797 mg, 87% yield).

$[a]_D^{25}$ –53.7 (*c* 0.26, $CHCl_3$); R_f = 0.25 (1:4 EtOAc:hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 5.79 (ddt, J = 17.3, 10.2, 7.2 Hz, 1H), 5.18 – 5.11 (m, 2H), 3.66 (dd, J = 9.9, 4.2 Hz, 1H), 3.54 – 3.51 (m, 1H), 3.48 (s, 1H), 3.34 (t, J = 5.8 Hz, 1H), 2.55 – 2.48 (m, 1H), 2.39 (dtt, J = 13.9, 6.7, 1.3 Hz, 1H), 1.19 (s, 9H), 0.89 (s, 9H), 0.05 (d, J = 0.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.5, 118.6, 77.2, 65.1, 56.5, 56.0, 37.2, 26.0, 22.7, 18.4, -

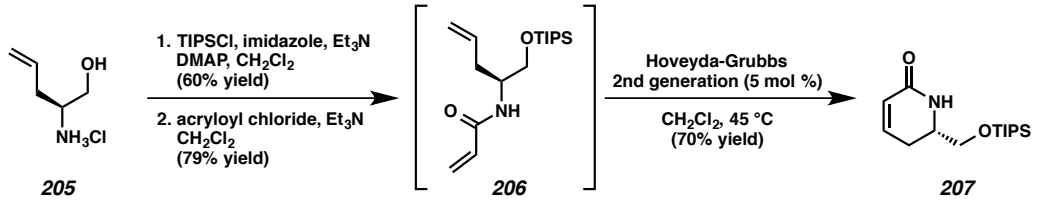
5.3, -5.3; IR (Neat Film NaCl) 2955, 2929, 2858, 1472, 1253, 1113, 1072, 836, 777 cm^{-1}; HRMS (MM: FAB+) *m/z* calc'd for $C_{15}H_{34}NO_2SSi$ $[M+H]^+$: 320.2001; found: 320.2084.



204 ***205***

To a solution of silyl ether **204** (126 mg, 0.394 mmol, 1.00 equiv) in MeOH (1.97 mL) was added 4N HCl in dioxane (1.97 mL, 1.97 mmol, 5.00 equiv) at 0 °C. The reaction mixture was warmed to 23 °C and stirred for 2 h. The volatile was evaporated under reduced pressure. The resulting oil was washed with ether revealing a yellow solid. The solid was filtered to give amine hydrochloride **205** (49.0 mg, 90% yield).

$[a]_D^{25}$ +9.52 (*c* 0.06, MeOH); R_f = 0.10 (2:1 EtOAc:hexane); ^1H NMR (500 MHz, CD_3OD) δ 5.81 (ddt, J = 17.3, 10.2, 7.2 Hz, 1H), 5.29 – 5.19 (m, 2H), 3.76 (dd, J = 11.6, 3.7 Hz, 1H), 3.55 (dd, J = 11.6, 6.7 Hz, 1H), 3.29 – 3.20 (m, 1H), 2.47 – 2.32 (m, 2H); ^{13}C NMR (126 MHz, CD_3OD) δ 133.28, 120.24, 61.92, 53.96, 34.90; IR (Neat Film NaCl) 3369, 2929, 1618, 1508, 1053, 928 cm^{-1}.



205 ***206*** ***207***

To a solution of amine hydrochloride **205** (188 mg, 1.37 mmol, 1.00 equiv) in CH_2Cl_2 (7.00 mL) were added Et_3N (0.38 mL, 2.74 mmol, 2.00 equiv), imidazole (930 mg, 13.7 mmol, 10.0 equiv), DMAP (8.40 mg, 0.0685 mmol, 0.05 equiv), and TIPSCl (0.59 mL,

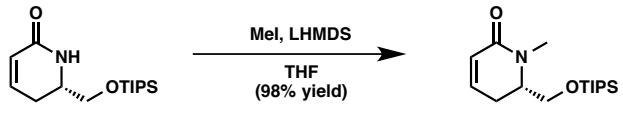
2.74 mmol, 2.00 equiv). The reaction mixture was stirred for 12 h at 23 °C and quenched with water. The aqueous phase was extracted with CH_2Cl_2 (3 x 8.00 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (2:1 EtOAc:hexane) to afford the silyl ether (212 mg, 60% yield).

To a solution of the resultant silyl ether (100 mg, 0.388 mmol, 1.00 equiv) and Et_3N (0.160 mL, 1.16 mmol, 3.00 equiv) in CH_2Cl_2 (1.94 mL) was added acryloyl chloride (35.0 μL, 0.427 mmol, 1.10 equiv) at 23 °C. The reaction was stirred for 12 h at 23 °C and quenched with water. The aqueous phase was extracted with CH_2Cl_2 (3 x 2.00 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (1:4 EtOAc:hexanes) to afford amide **206** (95.0 mg, 79% yield).

To a stirred solution of amide **206** (1.08 g, 3.47 mmol, 1.00 equiv) in CH_2Cl_2 (116 mL) was added Hoveyda-Grubbs 2nd generation catalyst (0.109 g, 0.173 mmol, 0.05 equiv) at 23 °C. Then, the solution was stirred at 45 °C for 12 h. After the reaction was done, the solution was cooled to 23 °C and water was added. The aqueous phase was extracted with CH_2Cl_2 (3 x 30.0 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (1:2 EtOAc:hexanes) to afford lactam **207** (688 mg, 70% yield).

$[a]_D^{25}$ –15.6 (*c* 0.22, $CHCl_3$); R_f = 0.20 (1:2 EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.58 (ddd, *J* = 9.9, 5.4, 3.0 Hz, 1H), 5.92 (dtd, *J* = 9.9, 2.4, 1.3 Hz, 1H), 5.87 (s, br, 1H), 3.80 – 3.72 (m, 2H), 3.66 – 3.58 (m, 1H), 2.31 (dtt, *J* = 17.6, 5.4, 1.2 Hz, 1H), 2.16 (ddt, *J* = 17.7, 10.9, 2.8 Hz, 1H), 1.21 – 1.00 (m, 21H); ^{13}C NMR (126 MHz, $CDCl_3$) δ

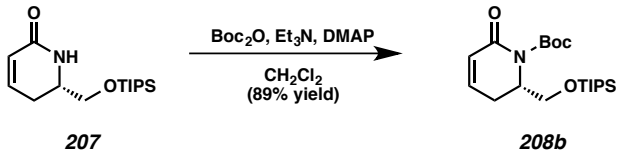
166.0, 140.0, 124.8, 66.0, 52.6, 26.0, 18.1, 12.0; IR (Neat Film NaCl) 2943, 2866, 1682, 1615, 1463, 1114, 813 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{15}H_{30}NO_2Si$ $[M+H]^+$: 284.2040; found: 284.2045.



207 ***208a***

To a solution of lactam **207** (100 mg, 0.353 mmol, 1.00 equiv) in THF (1.80 mL) was added LHMDS (89.0 mg, 0.530 mmol, 1.50 equiv) at 0 °C. The reaction was stirred for 1 h and then MeI (66.0 μL, 1.06 mmol, 3.00 equiv) was added. The solution was stirred for 4 h at 23 °C and quenched with sat. aq NH_4Cl. The aqueous phase was extracted with EtOAc (3 x 2.00 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (1:2 EtOAc:hexanes) to afford amide **208a** (103 mg, 98% yield).

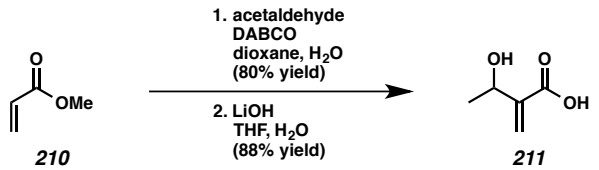
$[a]_D^{25}$ +46.9 (*c* 0.12, $CHCl_3$); R_f = 0.27 (1:2 EtOAc:hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 6.42 – 6.35 (m, 1H), 5.91 (ddd, J = 9.8, 2.7, 1.1 Hz, 1H), 3.74 (dd, J = 9.6, 5.2 Hz, 1H), 3.66 (dd, J = 9.6, 8.6 Hz, 1H), 3.55 – 3.48 (m, 1H), 3.05 (s, 3H), 2.58 (ddt, J = 6.8, 5.0, 2.0 Hz, 2H), 1.15 – 1.00 (m, 21H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.1, 137.3, 125.0, 61.6, 59.2, 34.3, 25.0, 18.1, 12.0; IR (Neat Film NaCl) 2942, 2866, 1670, 1618, 1464, 1111, 882 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{16}H_{32}NO_2Si$ $[M+H]^+$: 298.2197; found: 298.2199.



207 ***208b***

To a solution of amide **207** (50.0 mg, 0.176 mmol, 1.00 equiv) and DMAP (32.2 mg, 0.264 mmol, 1.50 equiv) in CH_2Cl_2 (0.90 mL) at 0 °C were added Et_3N (49.1 μL, 0.352 mmol, 2.00 equiv) and Boc anhydride (77.0 mg, 0.353 mmol, 2.00 equiv). The reaction mixture was warmed to 23 °C and stirred for 12 h. The reaction was quenched with sat. aq NH_4Cl. The aqueous phase was extracted with CH_2Cl_2 (3 x 1.00 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (1:8 EtOAc:hexanes) to afford carbamate **208b** (60.0 mg, 89% yield).

$[a]_D^{25}$ +11.5 (*c* 0.07, $CHCl_3$); R_f = 0.85 (1:2 EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.59 (ddt, J = 9.8, 6.3, 1.9 Hz, 1H), 5.94 (ddd, J = 9.8, 3.1, 0.8 Hz, 1H), 4.45 (ddt, J = 9.6, 4.8, 3.1 Hz, 1H), 3.74 (dd, J = 9.3, 4.8 Hz, 1H), 3.67 (t, J = 9.5 Hz, 1H), 2.76 (dd, J = 18.8, 6.3 Hz, 1H), 2.62 – 2.54 (m, 1H), 1.53 (s, 9H), 1.20 – 0.96 (m, 21H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.3, 152.3, 140.9, 126.0, 83.1, 77.2, 61.8, 54.6, 28.2, 24.8, 18.1, 12.0; IR (Neat Film NaCl) 2944, 2867, 1717, 1368, 1297, 1239, 1160, 1114, 810 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{15}H_{30}NO_2Si$ $[M+H–Boc]^+$: 284.2040; found: 284.2046.



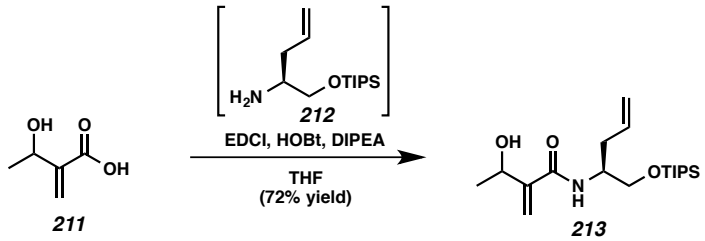
210 ***211***

To a solution of acetaldehyde (1.27 mL, 22.7 mmol, 1.00 equiv) in dioxane/water (1.10 mL/1.10 mL) was added methyl acrylate **210** (6.13 mL, 68.1 mmol, 3.00 equiv) and

DABCO (2.55 g, 22.7 mmol, 1.00 equiv). The reaction was stirred at 23 °C for 48 h. After the reaction was done, water was added. The aqueous phase was extracted with EtOAc (3 x 10.0 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (1:4 EtOAc:hexanes) to afford the ester (2.36 g, 80% yield). The spectroscopic data were identical to those previously reported.[2]

To a solution of the resultant ester (300 mg, 2.31 mmol, 1.00 equiv) in THF (12.0 mL) and H_2O (5.00 mL) at 23 °C was added LiOH (88.0 mg, 3.69 mmol, 1.60 equiv). The reaction was stirred at 23 °C for 1 h and then water was added. The aqueous phase was separated and acidified until pH = 1 with 1N HCl. Then, the aqueous phase was extracted with EtOAc (3 x 10.0 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to afford acid **211** (236 mg, 88% yield).

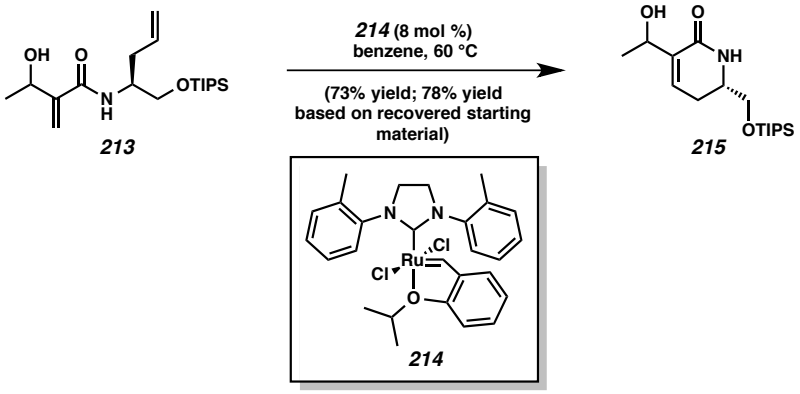
R_f = 0.15 (1:1 EtOAc:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.39 (t, *J* = 0.8 Hz, 1H), 5.96 (t, *J* = 1.1 Hz, 1H), 4.65 (q, J = 6.5 Hz, 1H), 1.42 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 142.8, 127.0, 67.1, 22.2; IR (Neat Film NaCl) 3390, 1694, 1633, 1416, 1277, 1176, 1093, 962, 928 cm^{-1}; HRMS (MM: FAB+) *m/z* calc'd for $C_5H_9O_3$ $[M+H]^+$: 117.0552; found: 117.0521.



[2] Latorre, A.; Sáez, J. A.; Rodríguez, S.; González, F. V. *Tetrahedron* **2014**, *70*, 97–102.

To a solution of amine **212** (50.0 mg, 0.194 mmol, 1.00 equiv) in THF (1.00 mL) were added acid **211** (24.0 mg, 0.204 mmol, 1.05 equiv), HOBt (39.3 mg, 0.291 mmol, 1.50 equiv), EDCI (45.2 mg, 0.291 mmol, 1.50 equiv), and DIPEA (41.0 μL. 0.233 mmol, 1.2 equiv). The reaction was stirred for 12 h at 23 °C and then quenched with sat. aq NH_4Cl. The aqueous phase was extracted with EtOAc (3 x 1.50 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (1:4 → 1:2 EtOAc:hexanes) to afford amide **213** (49.7 mg, 72% yield).

$[a]_D^{25}$ –29.5 (*c* 0.07, $CHCl_3$); R_f = 0.35 (1:2 EtOAc:hexanes); (due to the distinct presence of rotameric isomers, the ^{13}C NMR contained extra peaks. See the attached spectrum), ^1H NMR (400 MHz, $CDCl_3$) δ 6.65 (dd, *J* = 18.7, 8.7 Hz, 1H), 5.81 (ddtd, *J* = 17.2, 10.2, 7.1, 1.5 Hz, 1H), 5.65 (d, *J* = 6.5 Hz, 1H), 5.45 (s, br, 1H), 5.19 – 5.00 (m, 2H), 4.57 (qt, *J* = 6.5, 1.2 Hz, 1H), 4.10 (dddddd, *J* = 8.2, 6.9, 5.1, 3.9, 2.8, 1.2 Hz, 1H), 3.85 – 3.68 (m, 2H), 2.48 – 2.29 (m, 2H), 1.38 (d, *J* = 6.5 Hz, 3H), 1.16 – 1.02 (m, 21H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.7, 167.6, 147.24, 147.17, 134.80, 134.77, 118.0, 117.9, 117.9, 117.7, 69.2, 69.1, 64.12, 64.11, 50.13, 50.12, 36.09, 36.07, 21.94, 21.86, 18.1, 12.0; IR (Neat Film NaCl) 3305, 2943, 2866, 1655, 1618, 1542, 1534, 1460, 1118, 882, 788, 682 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{19}H_{38}NO_3Si$ $[M+H]^+$: 356.2615; found: 356.2624.

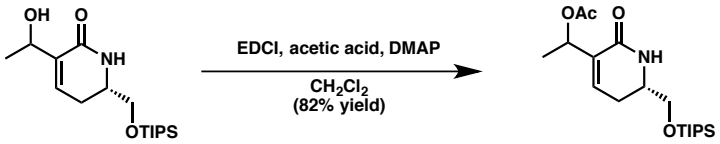


To a solution of amide **213** (740 mg, 2.08 mmol, 1.00 equiv) in benzene (104 mL) was added Ru catalyst **214** (95.0 mg, 0.17 mmol, 0.08 equiv). The solution was stirred at 60 °C for 12 h. The solvent was concentrated under reduced pressure. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) to furnish two diastereomers of lactam **215** (499 mg, 73% yield; 2:3 **215a**:**215b**; 78% yield based on recovered starting material).

Diastereomer **215a**: $[a]_D^{25}$ –1.54 (*c* 0.78, $CHCl_3$); R_f = 0.35 (1:1 EtOAc:hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 6.44 (ddd, *J* = 5.7, 3.0, 1.2 Hz, 1H), 5.93 (s, br, 1H), 4.62 – 4.55 (m, 1H), 3.75 (dd, *J* = 9.2, 4.3 Hz, 1H), 3.61 (dd, *J* = 9.2, 8.5 Hz, 1H), 2.38 – 2.31 (m, 1H), 2.22 – 2.15 (m, 1H), 1.38 (d, *J* = 6.5 Hz, 3H), 1.13 – 1.03 (m, 21H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.1, 137.0, 132.9, 66.7, 66.0, 52.3, 25.8, 21.1, 18.1, 12.0; IR (Neat Film NaCl) 3408, 2943, 2866, 1678, 1627, 1461, 1117, 1070, 882, 789, 683 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{17}H_{34}NO_3Si$ $[M+H]^+$: 328.2302; found: 328.2306.

Diastereomer **215b**: $[a]_D^{25}$ –1.77 (*c* 0.43, $CHCl_3$); R_f = 0.30 (1:1 EtOAc:hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 6.40 (dd, J = 5.8, 3.0 Hz, 1H), 5.92 (s, br, 1H), 4.54 (q, J = 6.5 Hz, 1H), 3.78 – 3.74 (m, 1H), 3.74 – 3.69 (m, 1H), 3.60 (t, J = 8.8 Hz, 1H), 2.31 (dt, J = 17.5, 5.5 Hz, 1H), 2.22 – 2.15 (m, 1H), 1.40 (d, J = 6.4 Hz, 3H), 1.13 – 1.04 (m, 21H);

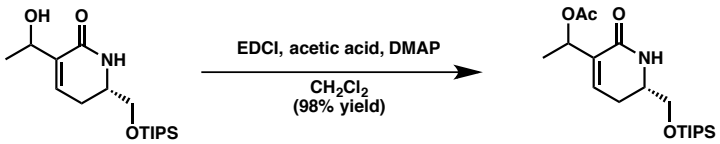
^{13}C NMR (126 MHz, $CDCl_3$) δ 166.9, 137.1, 133.2, 67.7, 66.0, 52.2, 25.8, 21.7, 18.1, 12.0; IR (Neat Film NaCl) 3294, 2943, 2866, 1678, 1627, 1463, 1115, 882 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{17}H_{34}NO_3Si$ $[M+H]^+$: 328.2302; found: 328.2303.



215a ***199a***

To a solution of EDCI (960 mg, 6.18 mmol, 10.0 equiv) and DMAP (38.0 mg, 0.309 mmol, 0.50 equiv) in CH_2Cl_2 (6.18 mL) was added acetic acid (0.354 mL, 6.18 mmol, 10.0 equiv). The solution was stirred for 5 min at 0 °C and then lactam **215a** (202 mg, 0.618 mmol, 1.00 equiv) in CH_2Cl_2 (0.5 mL) was added. The reaction mixture was stirred 12 h at 23 °C and then quenched with water. The aqueous phase was extracted with CH_2Cl_2 (3 x 4.50 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography with mixtures of EtOAc and hexanes to afford acetate **199a** (187 mg, 82% yield).

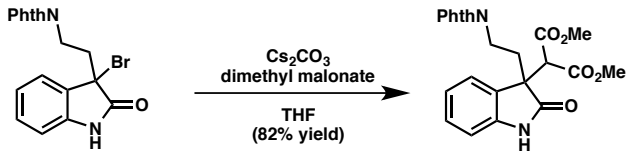
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.48 (ddd, *J* = 5.4, 3.3, 1.3 Hz, 1H), 6.06 (s, br, 1H), 5.78 (q, *J* = 6.6 Hz, 1H), 3.76 – 3.68 (m, 2H), 3.65 – 3.58 (m, 1H), 2.34 (dt, *J* = 17.5, 5.4 Hz, 1H), 2.26 – 2.15 (m, 1H), 2.07 (s, 3H), 1.40 (d, *J* = 6.5 Hz, 3H), 1.15 – 0.99 (m, 21H).



215b ***199b***

To a solution of EDCI (1.41 g, 9.07 mmol, 10.0 equiv) and DMAP (55.4 mg, 0.454 mmol, 0.50 equiv) in CH_2Cl_2 (9.07 mL) was added acetic acid (0.520 mL, 9.07 mmol, 10.0 equiv). The solution was stirred for 5 min at 0 °C and then lactam **215b** (297 mg, 0.907 mmol, 1.00 equiv) in CH_2Cl_2 (1.0 mL) was added. The reaction mixture was stirred 12 h at 23 °C and then quenched with water. The aqueous phase was extracted with CH_2Cl_2 (3 x 6.00 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography with mixtures of EtOAc and hexanes to afford acetate **199b** (328 mg, 98% yield).

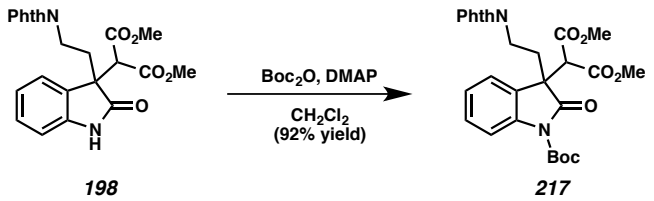
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.52 (ddd, *J* = 5.6, 3.2, 1.2 Hz, 1H), 6.07 (s, br, 1H), 5.77 – 5.69 (m, 1H), 3.72 (qd, *J* = 4.5, 2.0 Hz, 2H), 3.65 – 3.56 (m, 1H), 2.41 – 2.27 (m, 1H), 2.25 – 2.17 (m, 1H), 2.06 (s, 3H), 1.41 (d, *J* = 6.4 Hz, 3H), 1.14 – 1.00 (m, 21H).



216 ***198***

To a solution of bromooxindole **216** (3.60 g, 9.34 mmol, 1.00 equiv) and dimethyl malonate (2.62 mL, 28.0 mmol, 3.00 equiv) in THF (47.0 mL) was added Cs_2CO_3 (9.13 g, 28.0 mmol, 3.00 equiv). The reaction mixture was stirred for 12 h at 23 °C. After the reaction was done, water was added. The aqueous phase was extracted with EtOAc (3 x 15.0 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography with

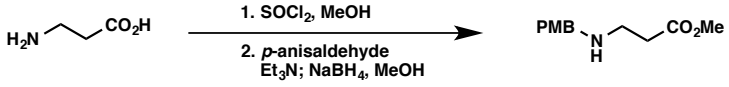
mixtures of EtOAc and hexanes to afford oxindole **198** (3.34 g, 82% yield). Data for the compound matches reported data.[3]



198 ***217***

To a solution of oxindole **198** (4.08 g, 9.34 mmol, 1.00 equiv) in CH_2Cl_2 (47.0 mL) were added DMAP (0.114 g, 0.934 mmol, 0.10 equiv) and Boc_2O (3.06 g, 14.0 mmol, 1.50 equiv). The reaction mixture was stirred for 12 h at 23 °C. Then, the reaction was quenched with water. The aqueous phase was extracted with CH_2Cl_2 (3 x 15.0 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography with mixtures of EtOAc and hexanes to afford carbamate **217** (4.61 g, 92% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 – 7.76 (m, 1H), 7.74 – 7.68 (m, 2H), 7.68 – 7.62 (m, 2H), 7.61 – 7.56 (m, 1H), 7.18 – 7.11 (m, 1H), 7.01 (td, *J* = 7.6, 1.2 Hz, 1H), 4.21 (s, 1H), 3.80 (s, 3H), 3.53 (t, *J* = 7.1 Hz, 2H), 3.49 (s, 3H), 2.51 (dt, *J* = 14.8, 7.5 Hz, 1H), 2.40 (dt, *J* = 13.8, 6.8 Hz, 1H), 1.65 (s, 9H).



222 ***SI-A11-1***

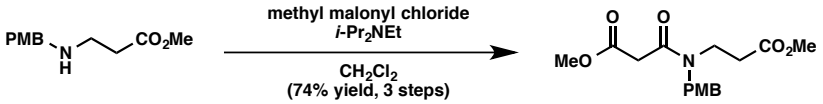
β-Alanine (**222**) (5.00 g, 56.1 mmol, 1.00 equiv) was added to MeOH (94.0 mL) and cooled to 0 °C before dropwise addition of $SOCl_2$ (8.19 mL, 0.112 mol, 2.00 equiv).

[3] Krishnan, S.; Stoltz, B. M. *Tetrahedron* **2007**, *48*, 7571–7573.

Then, the reaction was stirred for 2 h at 90 °C. The solution was concentrated under reduced pressure and treated with ether. The resulting crystals were removed by filtration to afford the ester, which was used without further purification.

To a solution of the resultant ester-HCl salt (2.00 g, 14.4 mmol, 1.00 equiv) and Et_3N (4.02 mL, 28.9 mmol, 2.00 equiv) in MeOH (40.0 mL) was added anisaldehyde (1.83 mL, 15.1 mmol, 1.05 equiv) and the reaction mixture was stirred for 1.5 h. Then, $NaBH_4$ (1.09 g, 28.8 mmol, 2.00 equiv) was added in portions in 1 h at 0 °C. The reaction was stirred at 23 °C for 8 h and then quenched with water. The aqueous phase was extracted with EtOAc (3 x 25.0 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to afford amine **SI-A11-1**.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 – 7.20 (m, 2H), 6.89 – 6.82 (m, 2H), 3.79 (s, 3H), 3.74 (s, 2H), 3.68 (s, 3H), 2.89 (t, *J* = 6.5 Hz, 2H), 2.54 (t, *J* = 6.5 Hz, 2H), 1.87 (s, br, 1H).

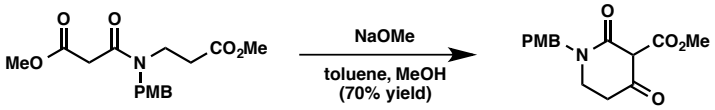


SI-A11-1 ***223***

To a solution of amine **SI-A11-1** (2.64 g, 11.8 mmol, 1.00 equiv) and *i*-Pr_2NEt (4.22 mL, 24.2 mmol, 2.05 equiv) in CH_2Cl_2 (59.0 mL) was added methyl malonyl chloride (2.02 mL, 18.9 mmol, 1.60 equiv) at °C. The solution was warmed to 23 °C and stirred for 1 h. Then, the reaction was quenched with sat. aq NH_4Cl. The aqueous phase was extracted with CH_2Cl_2 (3 x 25.0 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel

chromatography with mixtures of EtOAc and hexanes to afford amide **223** (2.82 g, 74% yield, 3 steps).

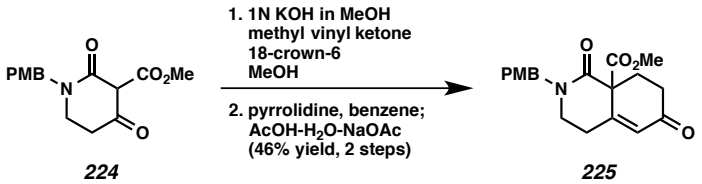
(Due to the distinct presence of rotameric isomers, the ^{1}H NMR contained extra peaks.) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.6 Hz, 1H), 7.14 – 7.06 (m, 1H), 6.93 – 6.87 (m, 1H), 6.87 – 6.82 (m, 1H), 4.57 (s, 1H), 4.52 (s, 1H), 3.80 (s, 2H), 3.79 (s, 1H), 3.76 (s, 1H), 3.72 (s, 2H), 3.68 – 3.58 (m, 5H), 3.52 (t, *J* = 7.1 Hz, 1H), 3.47 (s, 1H), 2.63 (t, *J* = 6.9 Hz, 1H), 2.54 (t, *J* = 7.1 Hz, 1H).



223 ***224***

To a solution of NaOMe (95%; 0.87 g, 15.2 mmol, 1.10 equiv) in toluene (69.0 mL) and MeOH (11.0 mL) was added amide **223** (2.81 g, 8.69 mmol, 1.00 equiv) in toluene (1.00 mL) dropwise. The solution was stirred at 90 °C for 6 h. The solution was cooled to 23 °C and water was added. The aqueous phase was extracted with EtOAc (3 x 25.0 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography with mixtures of EtOAc and hexanes to afford lactam **224** (1.78 g, 70% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 13.91 (s, 1H), 7.24 – 7.17 (m, 2H), 6.87 – 6.81 (m, 2H), 4.57 (s, 2H), 3.93 (s, 3H), 3.79 (s, 3H), 3.31 (t, *J* = 6.8 Hz, 2H), 2.57 (t, *J* = 6.8 Hz, 2H).



224 ***225***

To a stirred solution of lactam **224** (600 mg, 2.06 mmol, 1.00 equiv) in MeOH (1.60 mL) at 23 °C were added 1N KOH solution in MeOH (0.21 mL, 0.206 mmol, 0.10 equiv) and 18-crown-6 (54.0 mg, 0.206 mmol, 0.10 equiv) under N_2. After stirring for 10 min, methyl vinyl ketone (0.55 mL, 6.80 mmol, 3.30 equiv) was added dropwise at 23 °C and stirred for 22 h. The reaction mixture was concentrated under reduced pressure and the resulting residue was treated with sat. aq KCl solution. The aqueous phase was extracted with EtOAc (3 x 3.00 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to afford the ketone, which was used without further purification.

To a stirred solution of the resultant ketone (2.06 mmol, 1.00 equiv) in benzene (20.6 mL) was added pyrrolidine (0.43 mL, 5.15 mmol, 2.50 equiv) and the mixture was stirred at 90 °C for 6 h using Dean-Stark apparatus. The solution was cooled to 23 °C. The reaction mixture was treated with a mixture of AcOH/H_2O/NaOAc (2/2/1) (7.92 mL) and stirred at 100 °C for 3 h. The solution was cooled to 23 °C and treated with H_2O. The aqueous phase was extracted with EtOAc (3 x 25.0 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography with mixtures of EtOAc and hexanes to afford bicycle **225** (325 mg, 46% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 – 7.08 (m, 2H), 6.94 – 6.77 (m, 2H), 4.73 (d, *J* = 14.5 Hz, 1H), 4.41 (d, *J* = 14.5 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.38 (ddd, *J* = 12.1, 6.3, 3.9 Hz, 1H), 3.24 (ddd, *J* = 12.2, 9.9, 4.6 Hz, 1H), 3.04 – 2.96 (m, 1H), 2.90 – 2.77 (m, 1H), 2.59 – 2.43 (m, 2H), 2.18 – 2.10 (m, 1H), 2.08 – 2.04 (m, 1H).

225 ***226***

To a solution bicycle **225** (28.0 mg, 0.0815 mmol, 1.00 equiv) in *t*-BuOH (2.04 mL) were added AcOH (0.2 mL) and SeO_2 (18.1 mg, 16.3 mmol, 2.00 equiv). The reaction was stirred for 12 h at 100 °C. Solids were removed via a filtration through a celite plug and the resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography, using mixture of hexanes and ethyl acetate as eluent to furnish dienone **226** (11.1 mg, 40% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 10.1, 0.5 Hz, 1H), 7.24 – 7.19 (m, 2H), 6.90 – 6.85 (m, 2H), 6.45 (ddd, *J* = 10.1, 1.7, 0.6 Hz, 1H), 6.26 (td, *J* = 1.7, 0.7 Hz, 1H), 4.89 (d, *J* = 14.6 Hz, 1H), 4.28 (d, *J* = 14.6 Hz, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.42 (ddd, *J* = 12.1, 7.0, 3.6 Hz, 1H), 3.26 (ddd, *J* = 12.2, 9.5, 5.6 Hz, 1H), 2.96 (dddd, *J* = 14.6, 9.3, 7.0, 1.9 Hz, 1H), 2.63 (ddd, *J* = 14.5, 5.6, 3.6 Hz, 1H).

A11.4. References and Notes

(1) Zhu, G.-Y.; Yao, X.-J.; Liu, L.; Bai, L.-P.; Jiang, Z.-H. *Org. Lett.* **2014**, *16*, 1080–1083.

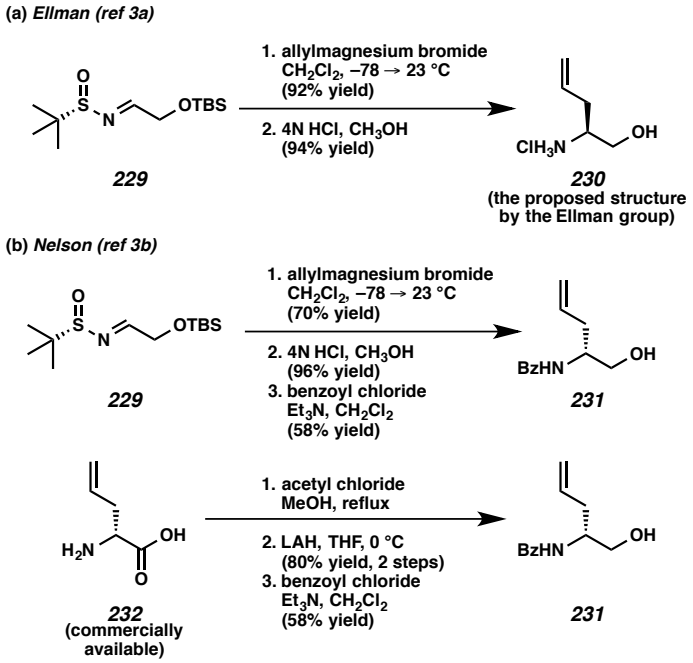
(2) (a) Shang, J. H.; Cai, X. H.; Feng, T.; Zhao, Y. L.; Wang, J. K.; Zhang, L. Y.; Yan, M.; Luo, X. D. *J. Ethnopharmacol.* **2010**, *129*, 174–181. (b) Shang, J.; H.; Cai, X. H.; Zhao, Y. L.; Feng, T.; Luo, X. D. *J. Ethnopharmacol.* **2010**, *129*, 293–298. (c) Baliga, M. S. *Integr. Cancer Ther.* **2010**, *9*, 261–269. (d) Lee, S. J.; Cho, S. A.; An, S. S.; Na, Y. J.;

Park, N. H.; Kim, H. S.; Lee, C. W.; Kim, H. K.; Kim, E. K.; Jang, Y. P.; Kim, J. W. *Evid. Based Complement Alternat. Med.* **2012**, *2012*, 190370.

(3) Horning, B. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, *135*, 6442–6445.

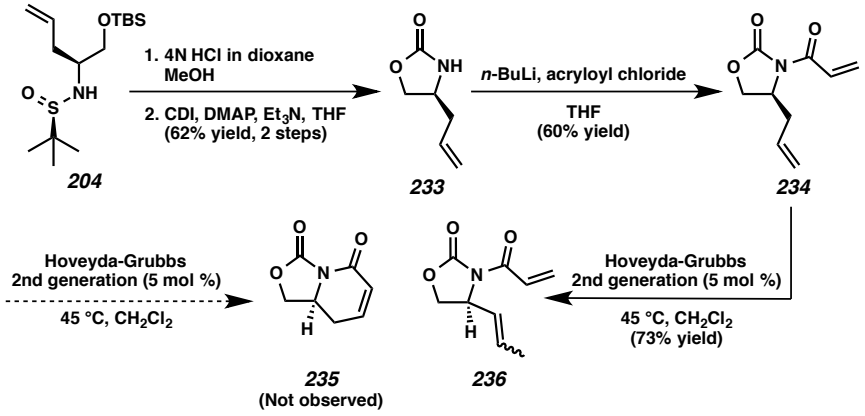
(4) (a) Rech, J. C.; Yato, M.; Duckett, D.; Ember, B.; LoGrasso, P. V.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 490–491. (b) Maurya, S. K.; Dow, M.; Warriner, S.; Nelson, A. *Beilstein J. Org. Chem.* **2013**, *9*, 775–785. (c) Koriyama, Y.; Nozawa, A.; Hayakawa, R.; Shimizu, M. *Tetrahedron* **2002**, *58*, 9621–9628.

(5) Although the Ellman group reported that allylmagnesium bromide was added from the *Si*-face of (*S*)-*tert*-butylsulfinyl imine **229** to deliver **230** (ref 3a), the opposite configuration was later confirmed by the Nelson group (ref 3b). The Nelson group prepared (*R*)-benzamide **231** from both the commercially available (*R*)-2-amino-4-pentenoic acid (**232**) and using Ellman's method with (*S*)-*tert*-butanesulfinamide. Then they discovered that the retention time of both benzamides (**231**) was identical on chiral HPLC.



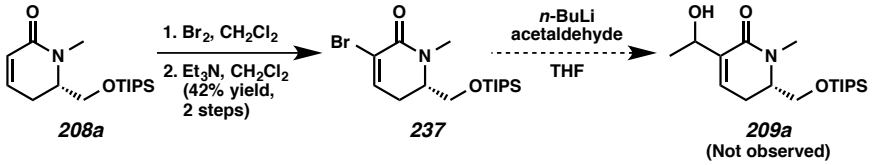
(6) (a) Donohoe, T. J.; Fishlock, L. P.; Procopiou, P. A. *Org. Lett.* **2008**, *10*, 285–288. (b) Hoffmann, T.; Lanig, H.; Waibel, R.; Gmeiner, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 3361–3364. (c) Huwe, C. M.; Kiehl, O. C.; Blechert, S. Synlett 1996, 65–66.

(7) Acidic removal of the silyl and *tert*-butanesulfinyl groups of **204** followed by carbamate formation with CDI afforded **233**. Although acylation of **233** generated metathesis precursor **234**, attempted ring-closing metathesis with Hoveyda-Grubbs 2nd generation catalyst to form bicycle **235** led only to double bond isomerization, generating **236**.



(8) (a) Latorre, A.; Sáez, J. A.; Rodríguez, S.; González, F. V. *Tetrahedron* **2014**, *70*, 97–102. (b) Rao, V. R.; Muthenna, P.; Shankaraiah, G.; Akileshwari, C.; Babu, K. H.; Suresh, G.; Babu, K. S.; Kumar, R. S. C.; Prasad, K. R.; Yadav, P. A.; Petrash, J. M.; Reddy, G. B.; Rao, J. M. *Eur. J. Med. Chem.* **2012**, *57*, 344–361. (c) Lee, K. C.; Loh, T. P. *Chem. Commun.* **2006**, *40*, 4209–4211.

(9) Although a-bromination of lactam **208a** produced bromide **237**, attempts to prepare the desired alcohol **209a** from bromide **237** were unsuccessful.



(10) The same result of the ring-closing metathesis of amide **213** was obtained with Hoveyda-Grubbs 2nd generation catalyst.

(11) (a) Krishnan, S.; Stoltz, B. M. *Tetrahedron Lett.* **2007**, *48*, 7571–7573. (b) Ma, S.; Han, X.; Krishnan, S.; Virgil, S. C.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 8037–8041.

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(13) Pereira, J.; Barlier, M.; Guillou, C. *Org. Lett.* **2007**, *9*, 3101–3103.

APPENDIX 12

Spectra Relevant to Appendix 11:

Synthetic Studies Toward Alistonitrine A

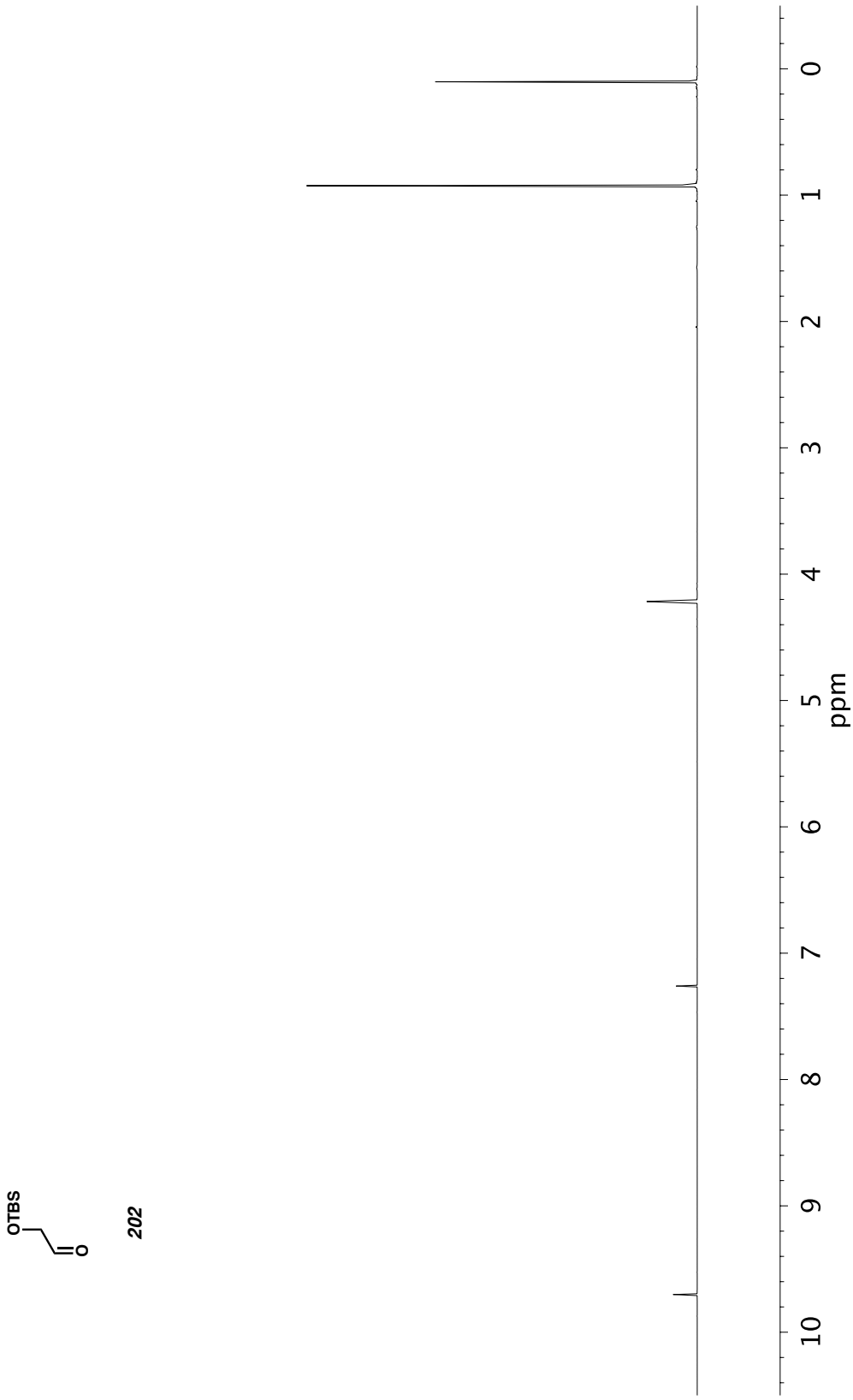

Figure A12.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **202**.

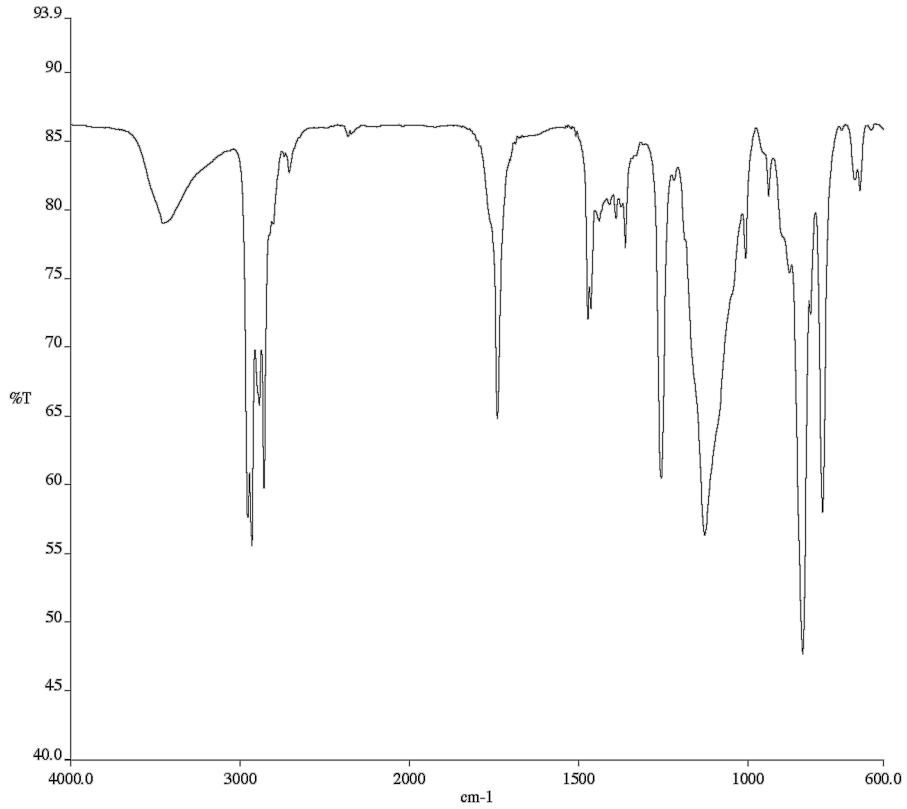

Figure A12.2. Infrared spectrum (Thin Film, NaCl) of compound **202**.

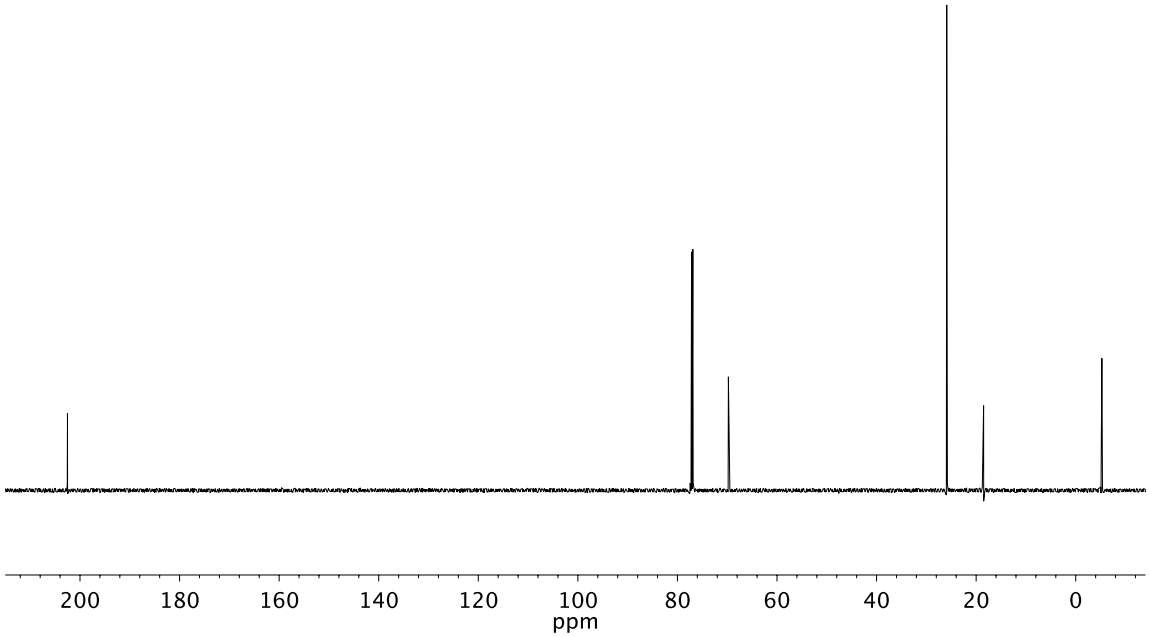

Figure A12.3. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **202**.

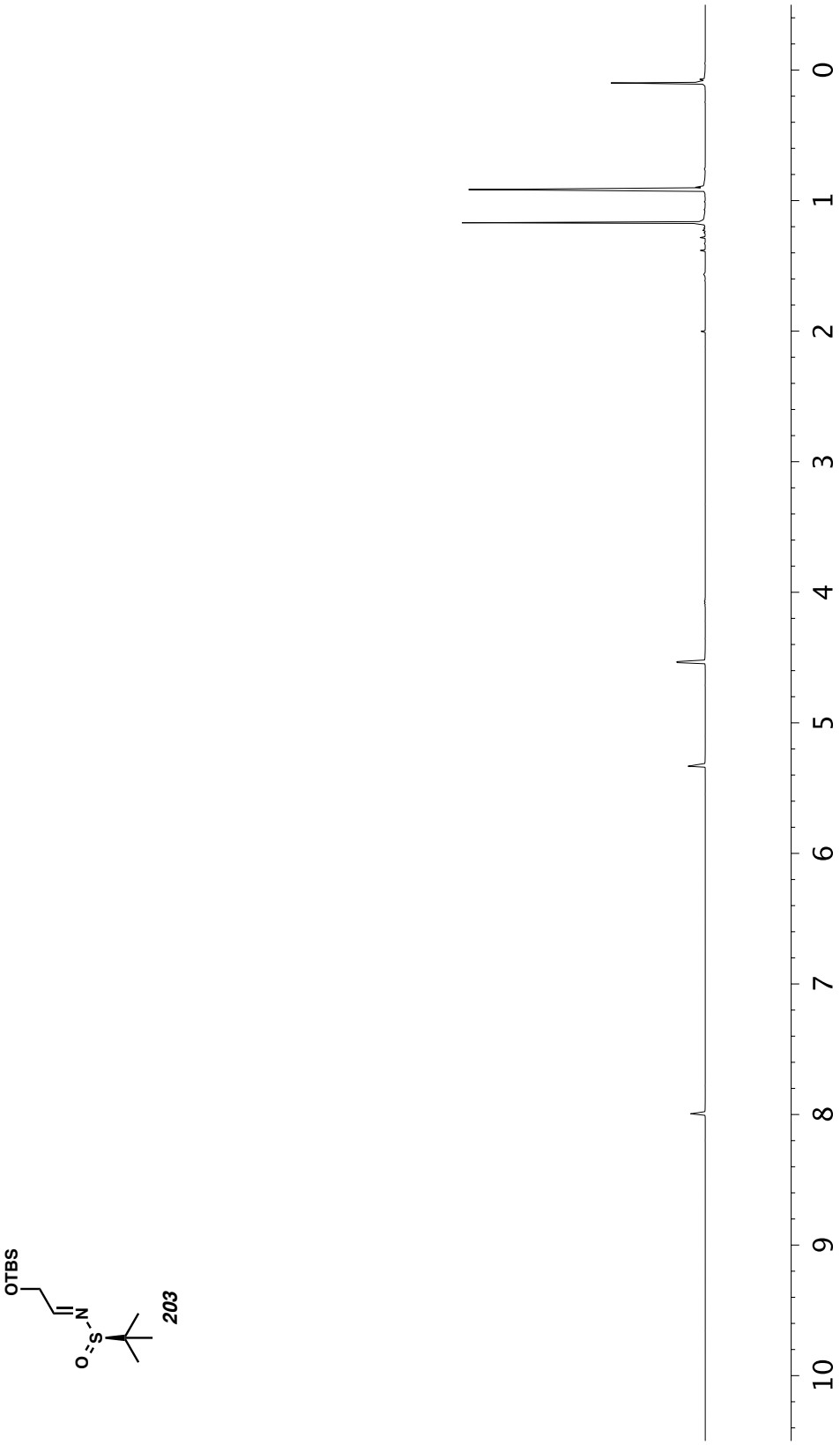

Figure A12.4. ^{1}H NMR (400 MHz, CD_2Cl_2) of compound **203**.

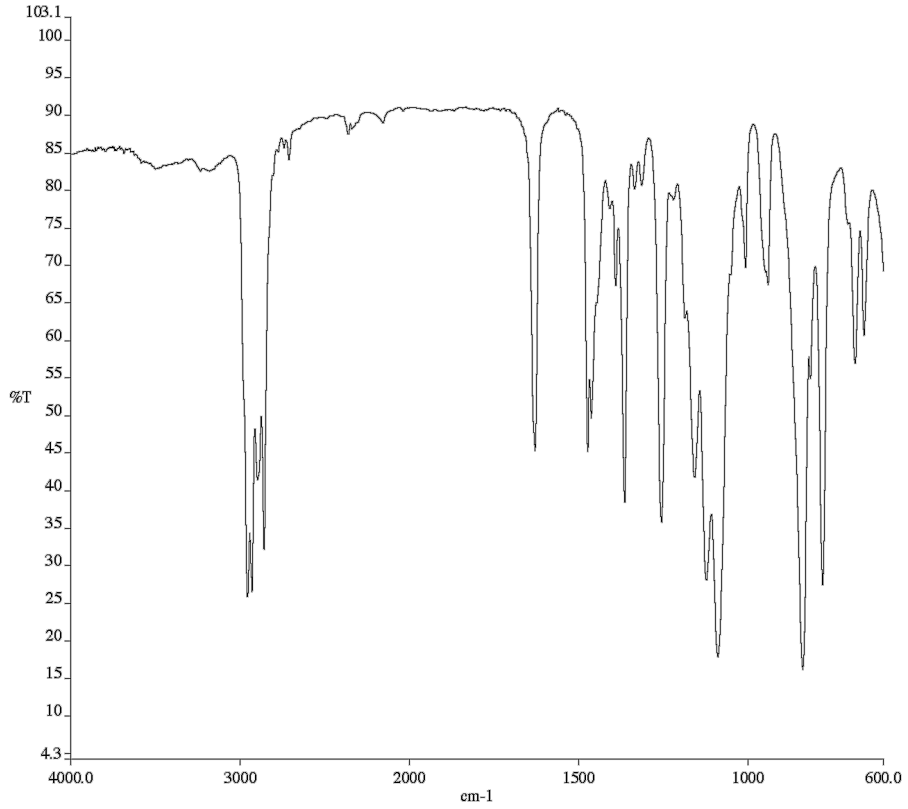

Figure A12.5. Infrared spectrum (Thin Film, NaCl) of compound **203**.

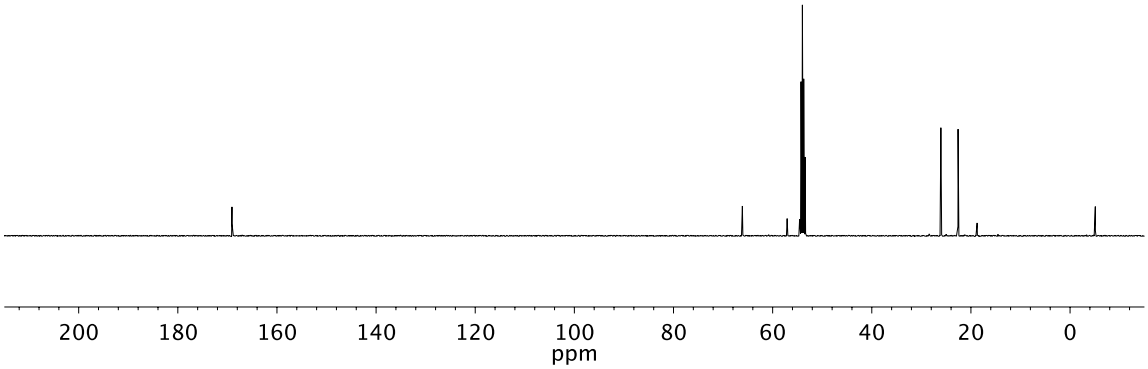

Figure A12.6. ^{13}C NMR (101 MHz, CD_2Cl_2) of compound **203**.

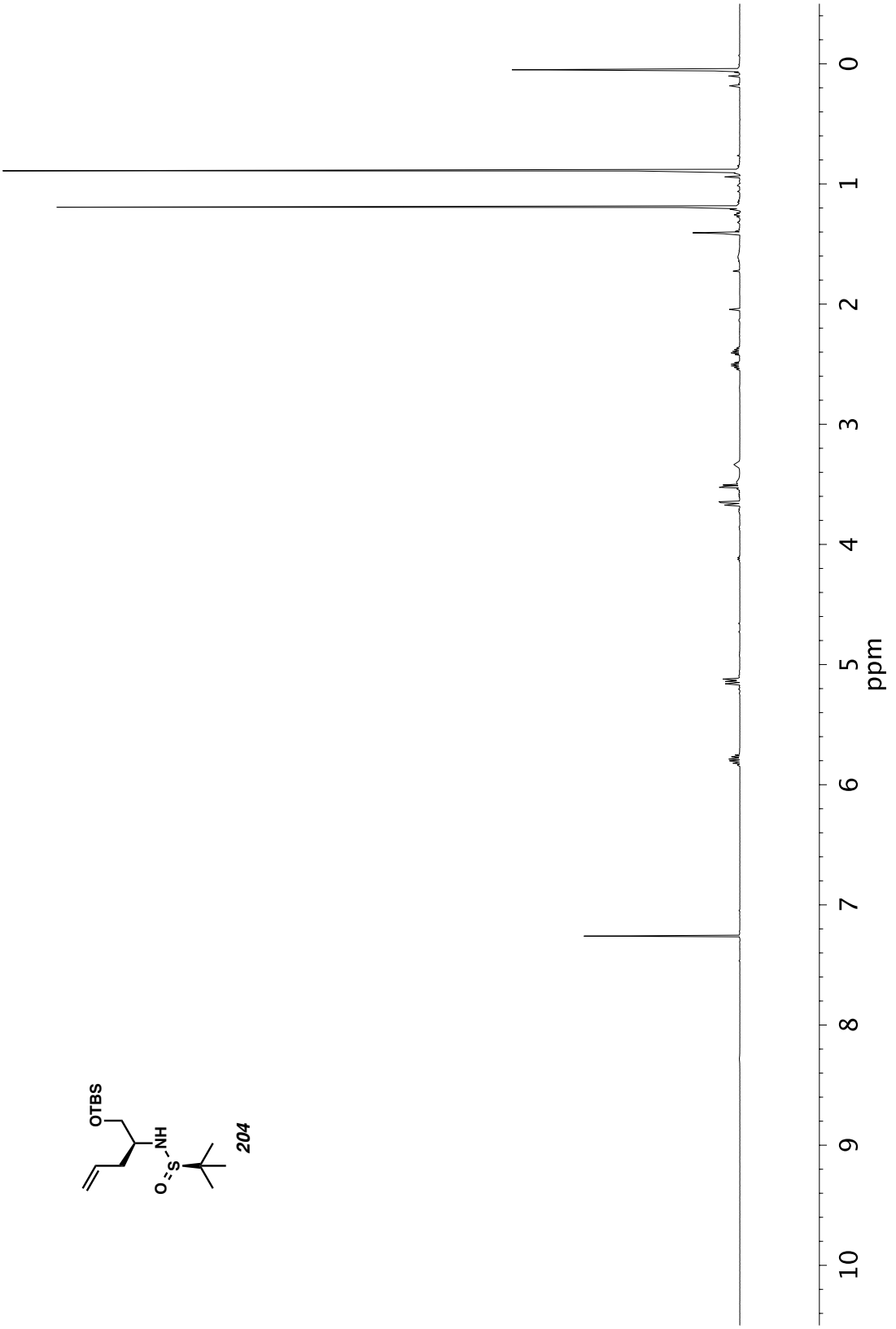

Figure A12.7. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **204**.

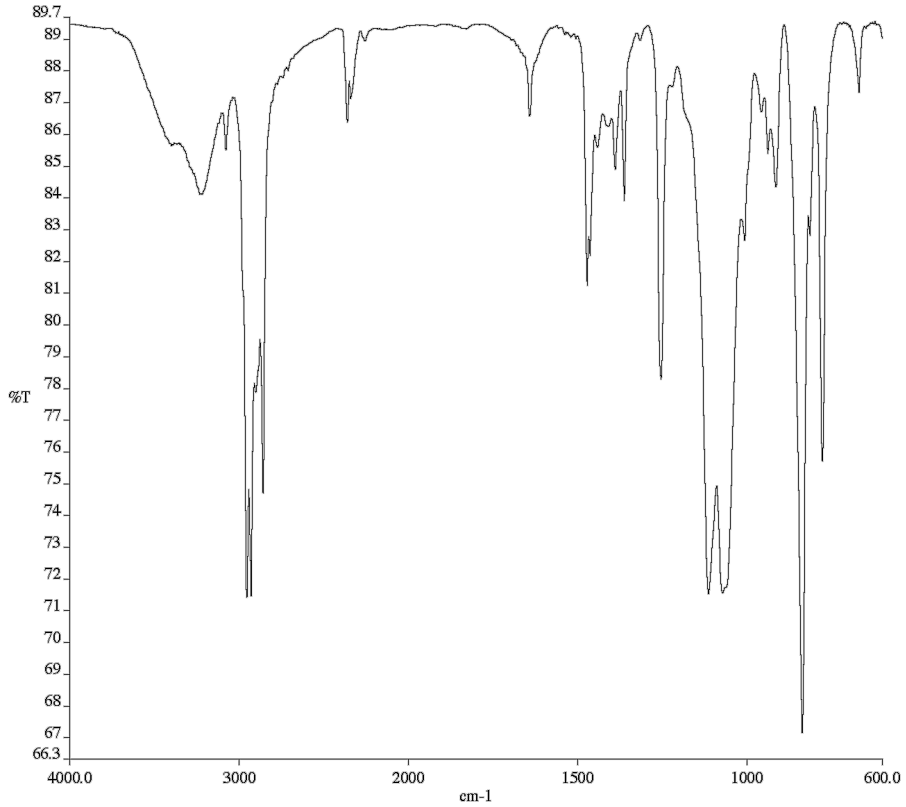

Figure A12.8. Infrared spectrum (Thin Film, NaCl) of compound **204**.

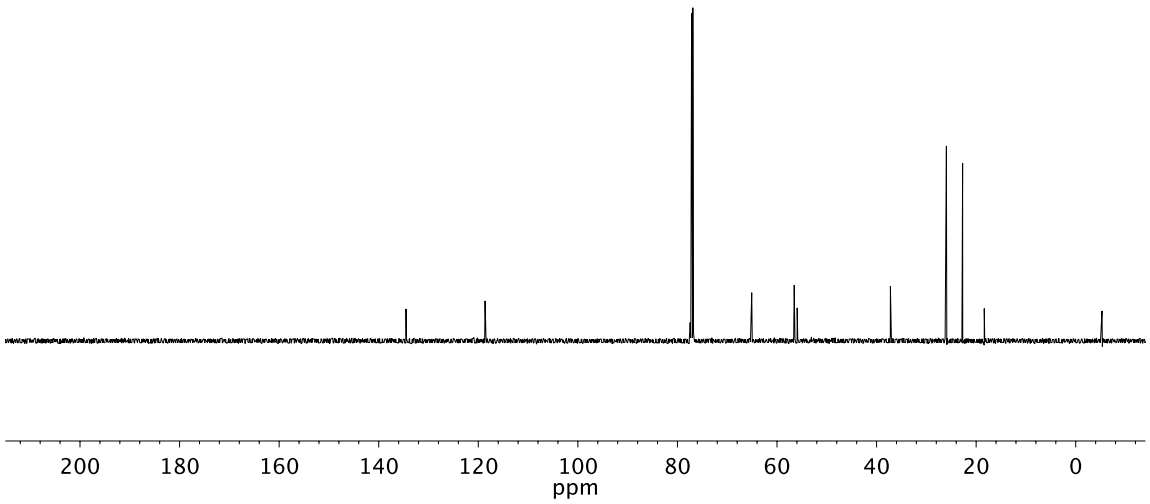

Figure A12.9. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **204**.

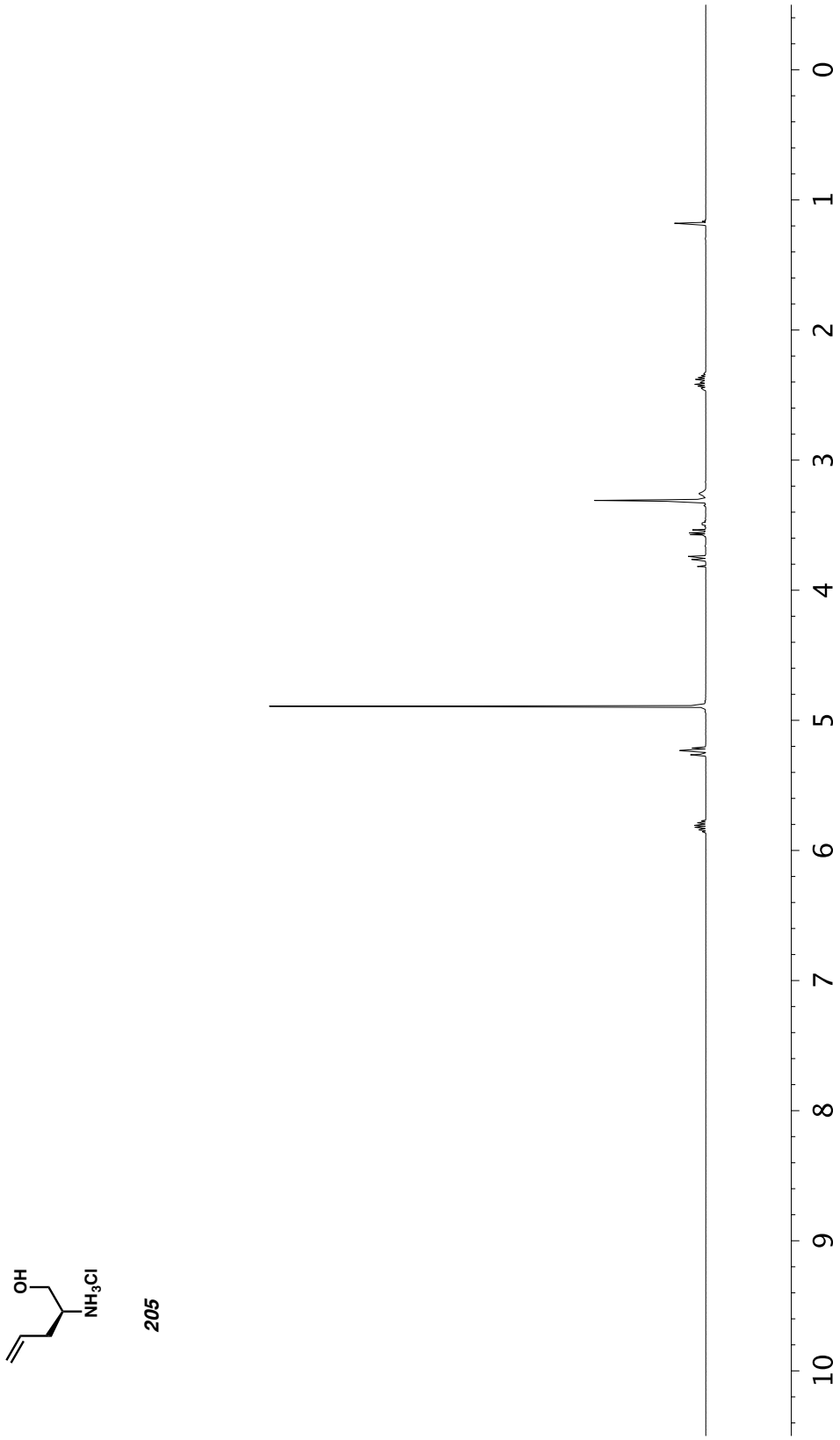

Figure A12.10. ^{1}H NMR (500 MHz, CD_3OD) of compound **205**.

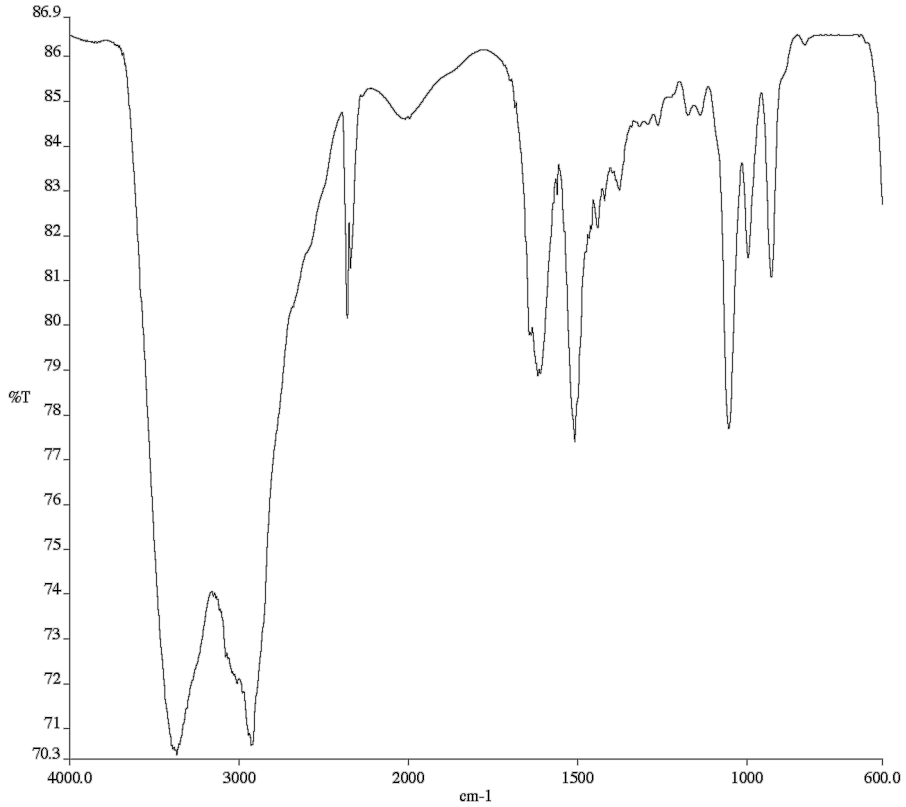

Figure A12.11. Infrared spectrum (Thin Film, NaCl) of compound **205**.

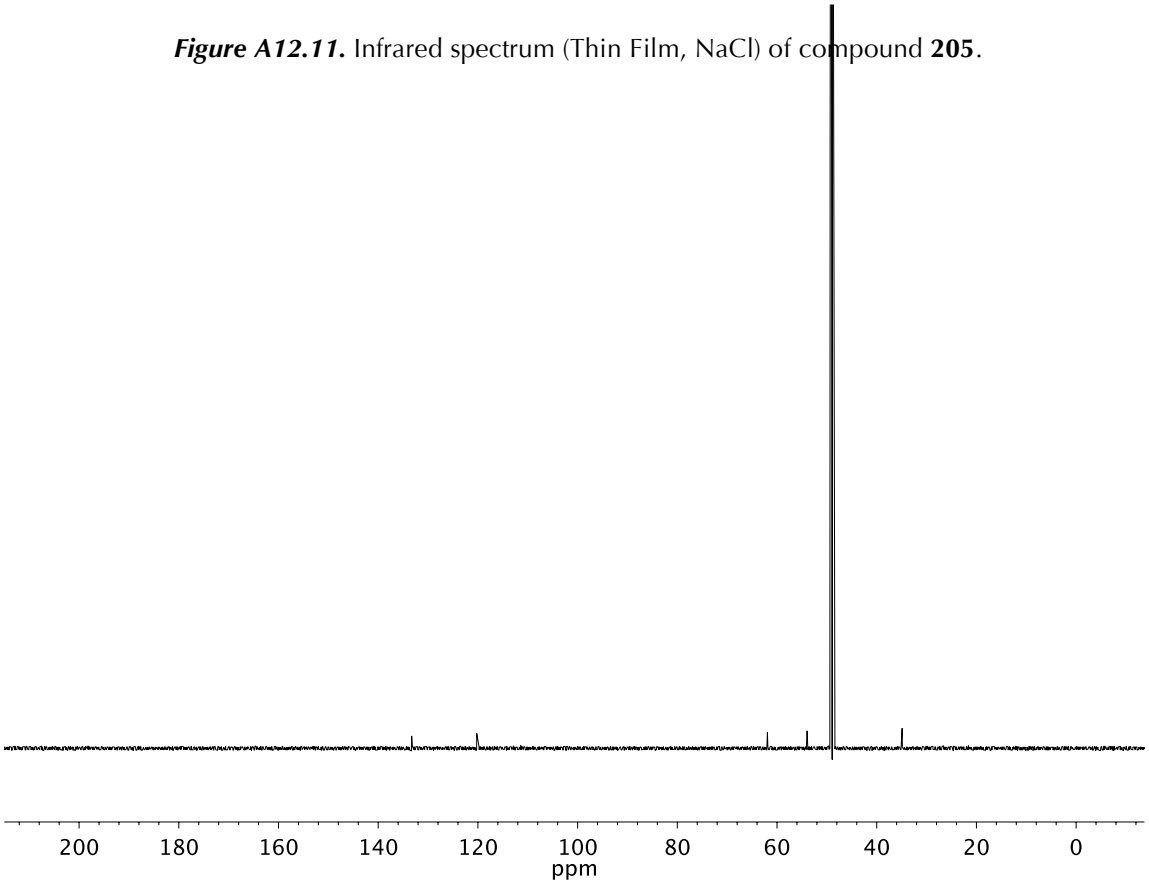

Figure A12.12. ^{13}C NMR (126 MHz, CD_3OD) of compound **205**.

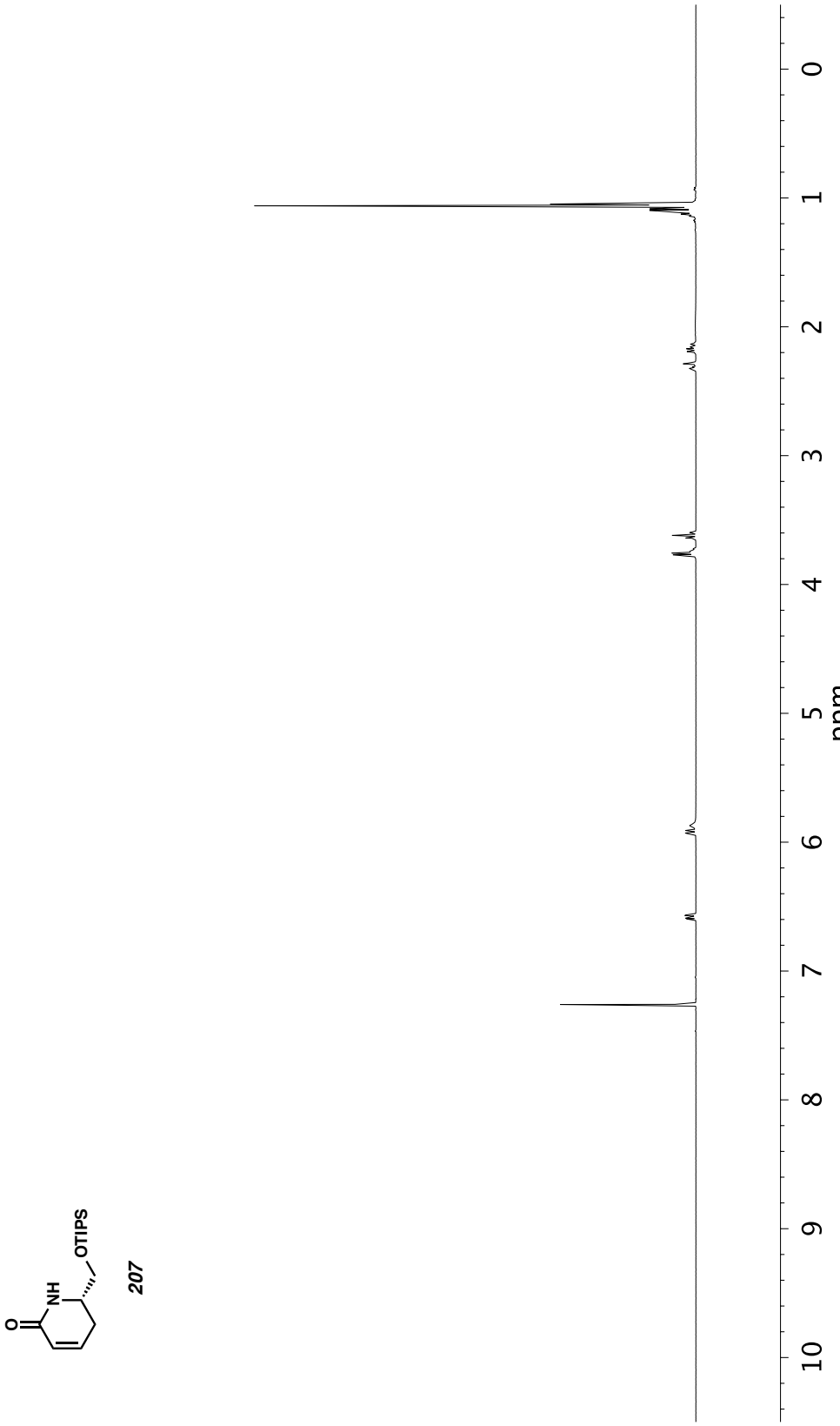

Figure A12.13. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **207**.

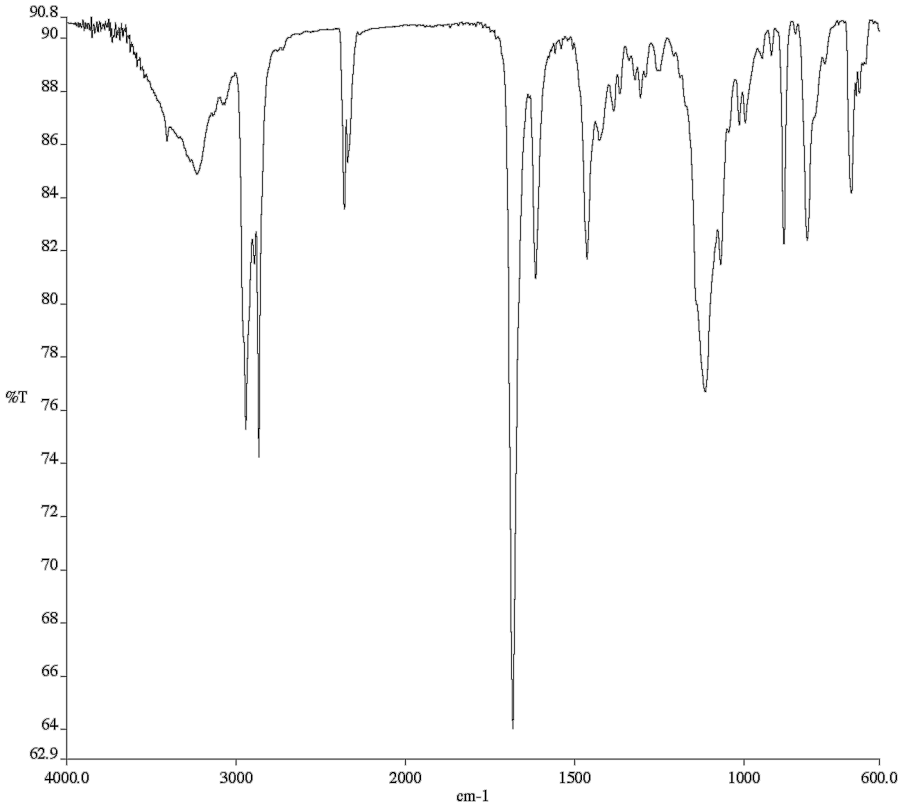

Figure A12.14. Infrared spectrum (Thin Film, NaCl) of compound **207**.

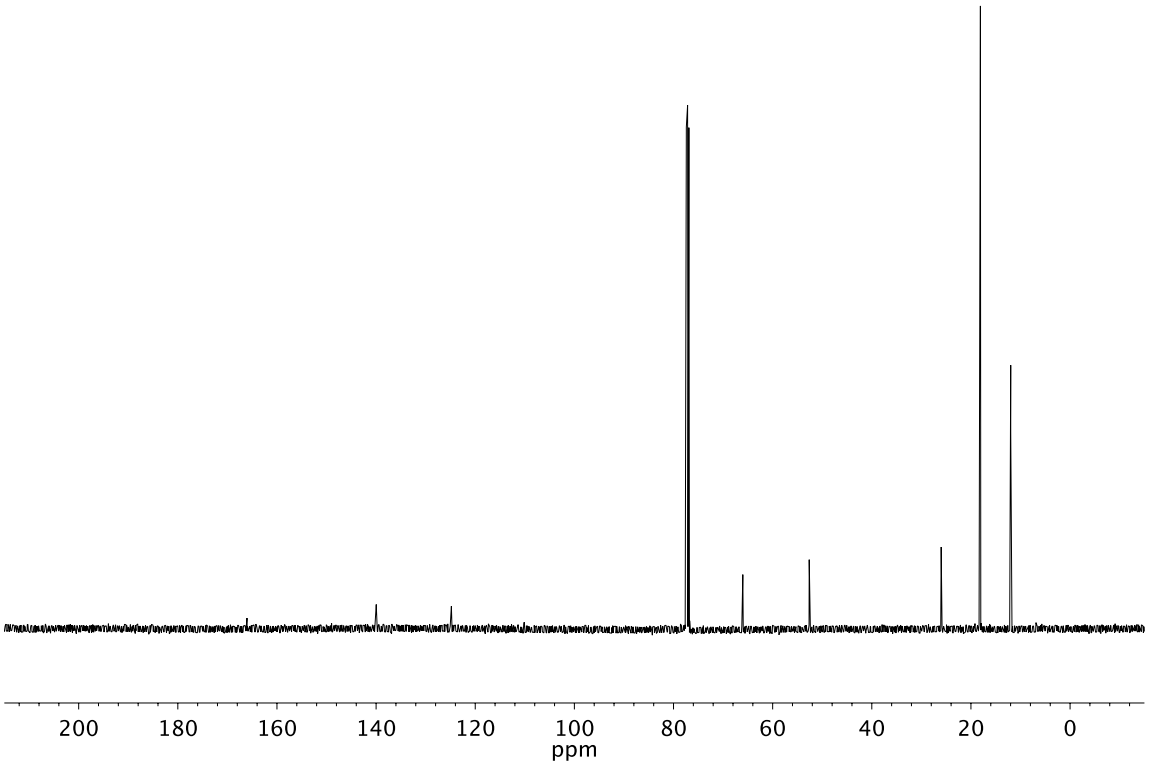

Figure A12.15. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **207**.

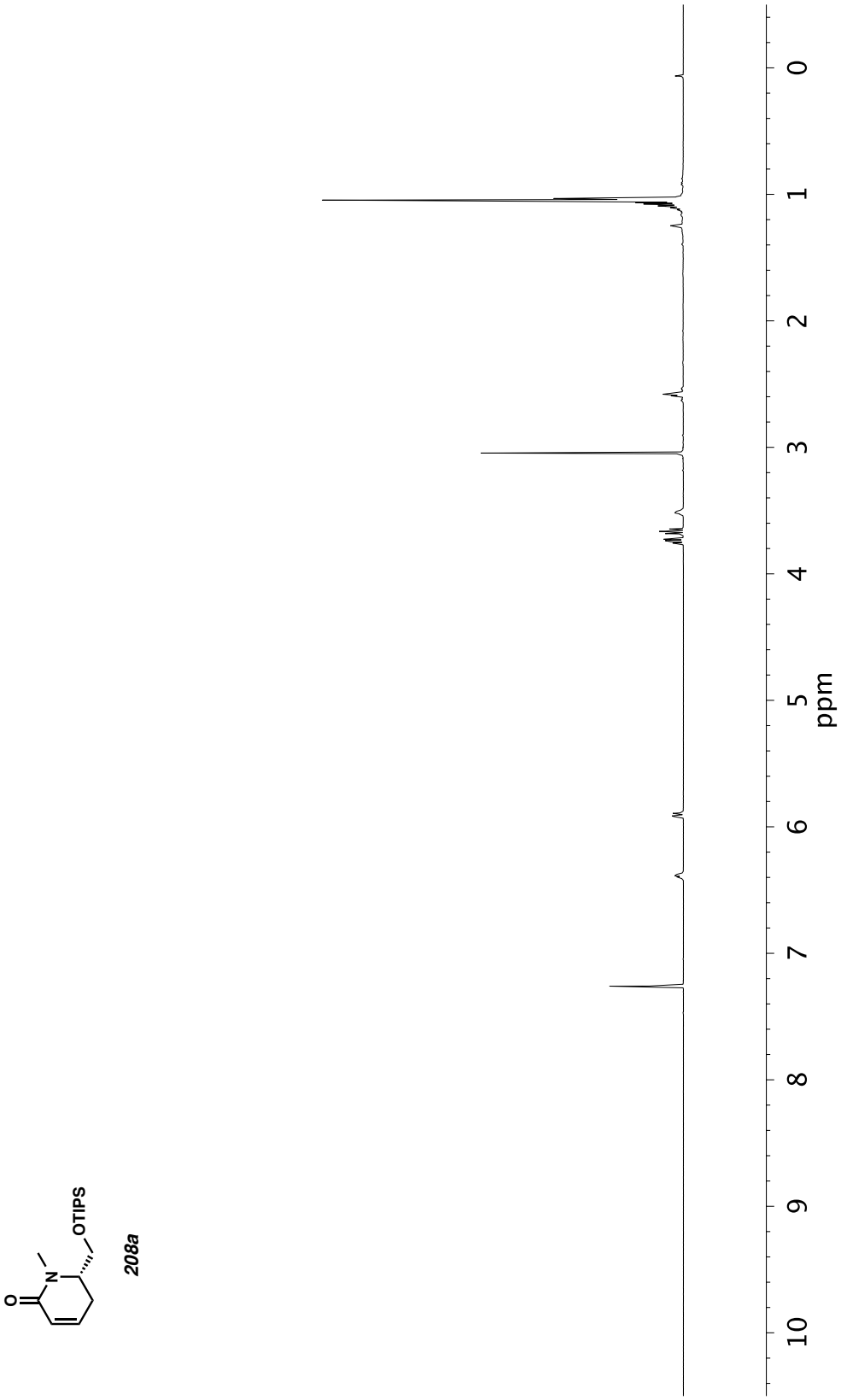

Figure A12.16. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **208a**.

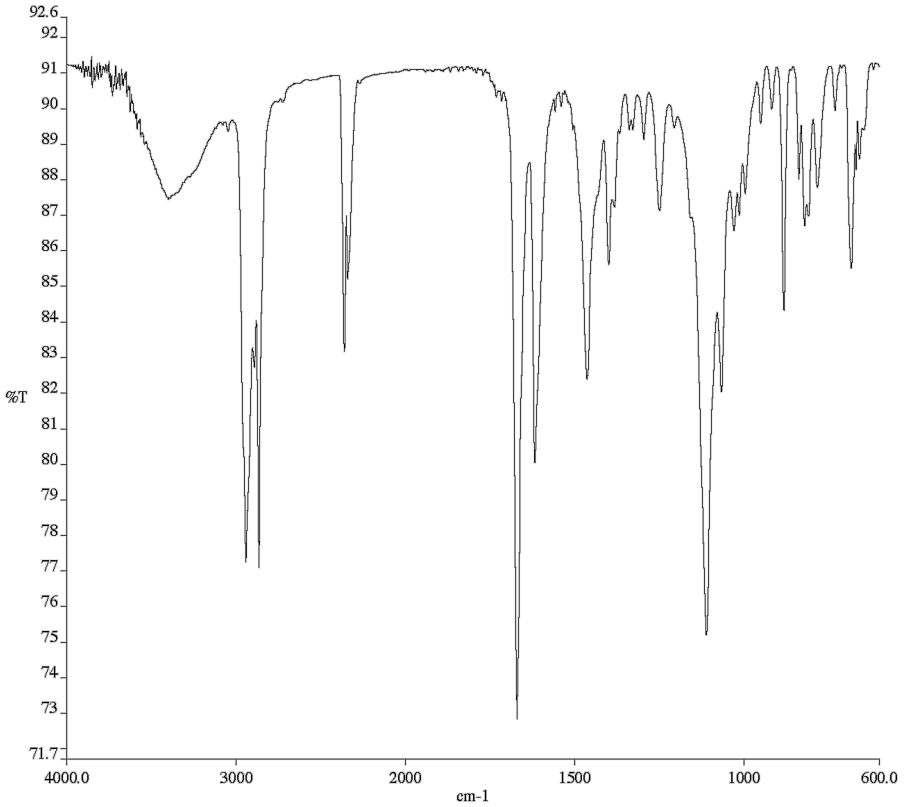

Figure A12.17. Infrared spectrum (Thin Film, NaCl) of compound **208a**.

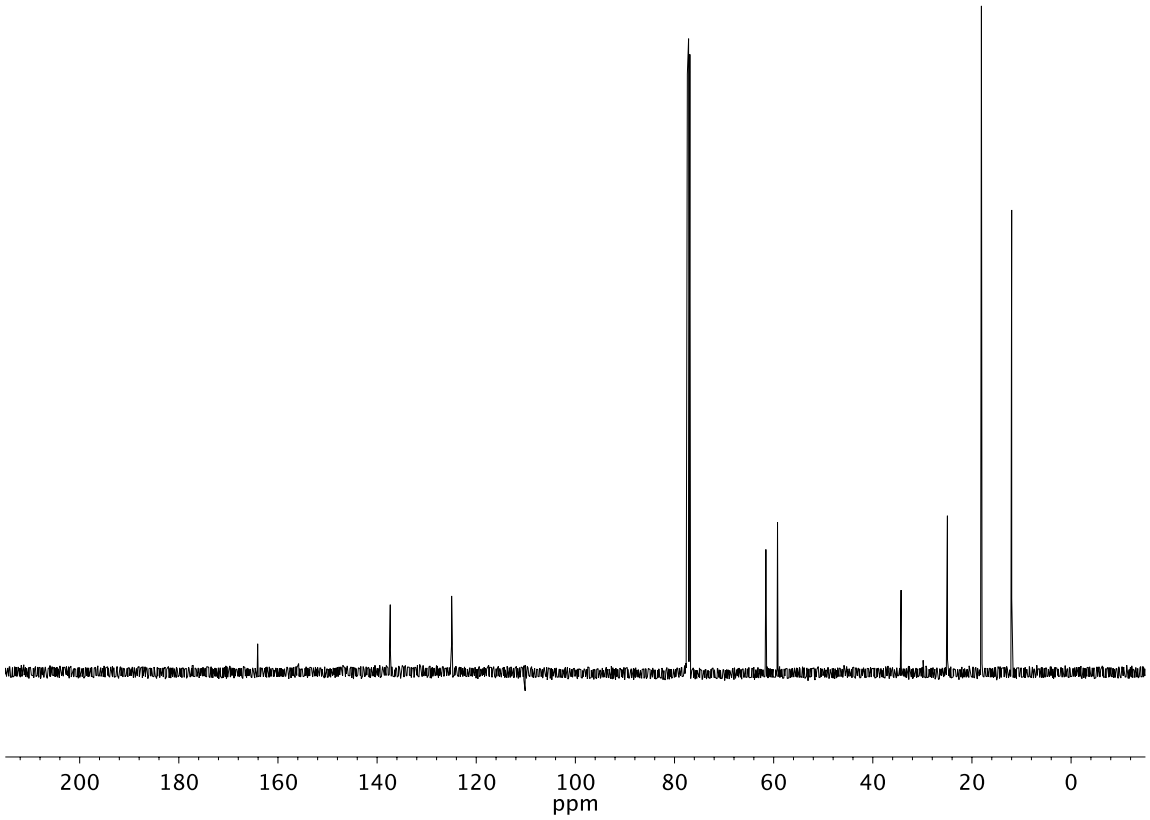

Figure A12.18. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **208a**.

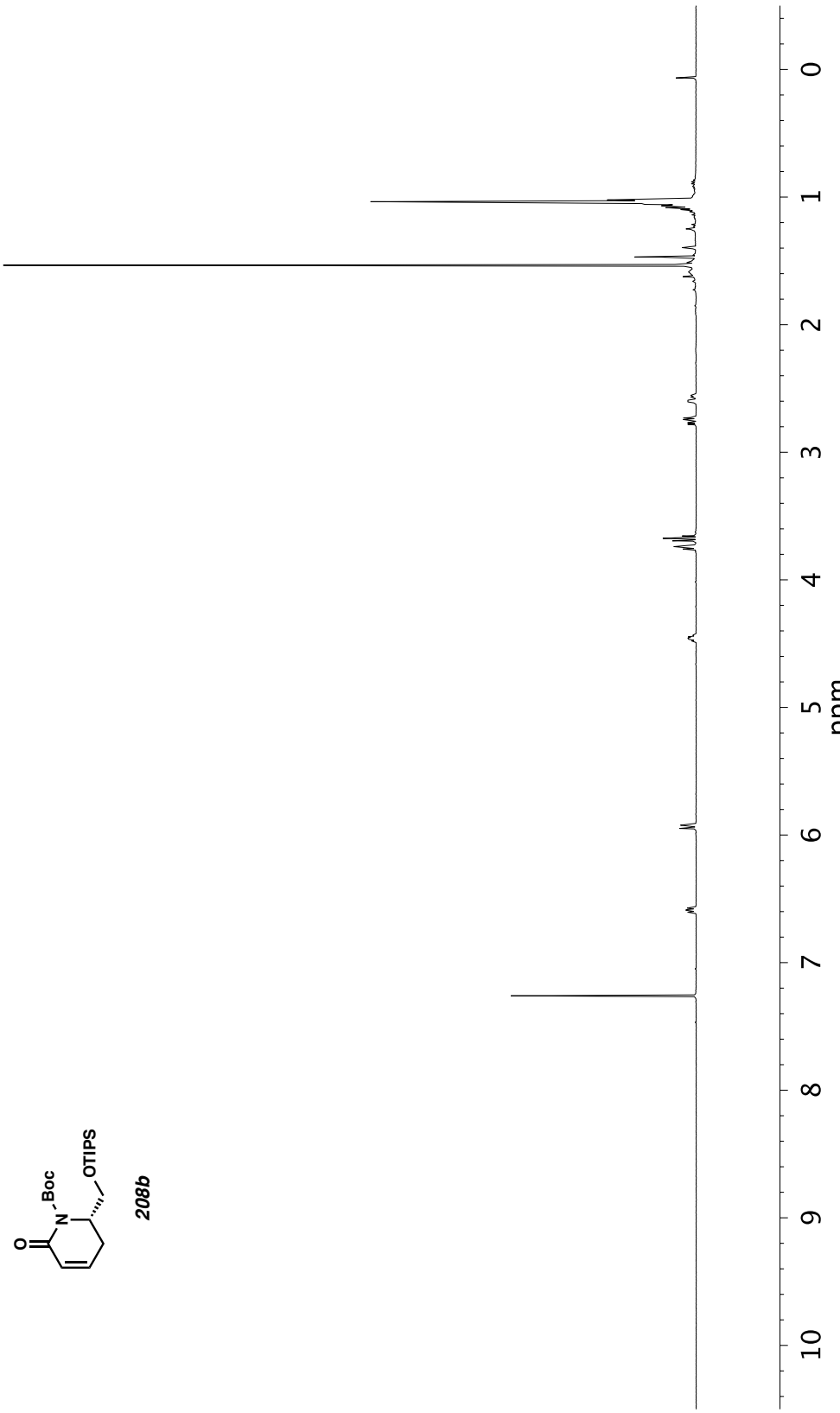

Figure A12.19. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **208b**.

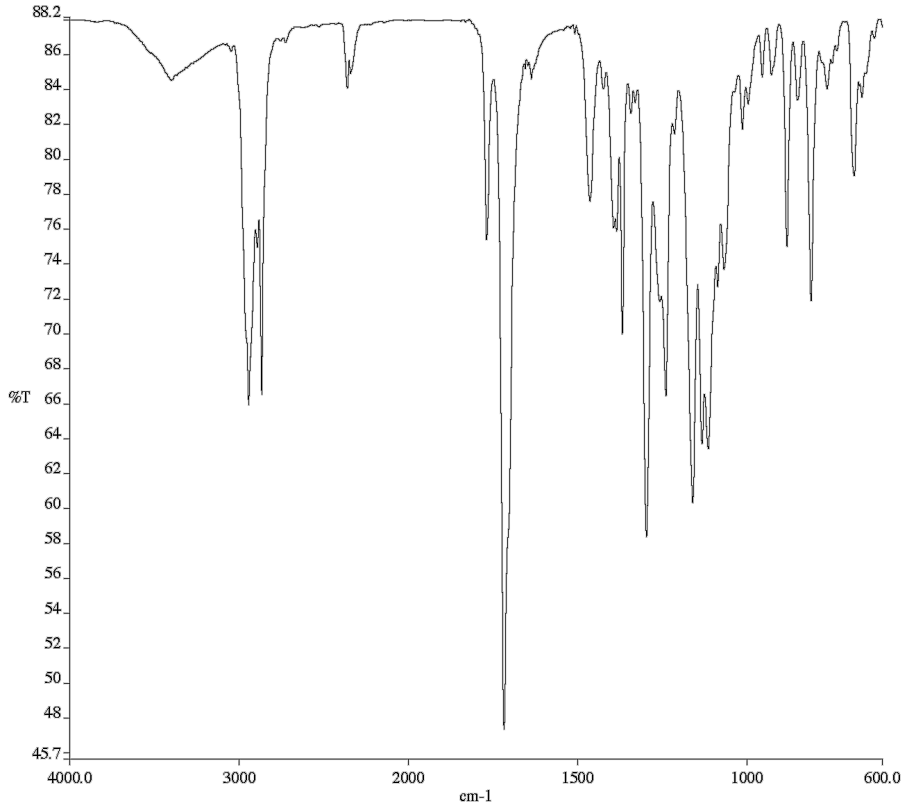

Figure A12.20. Infrared spectrum (Thin Film, NaCl) of compound **208b**.

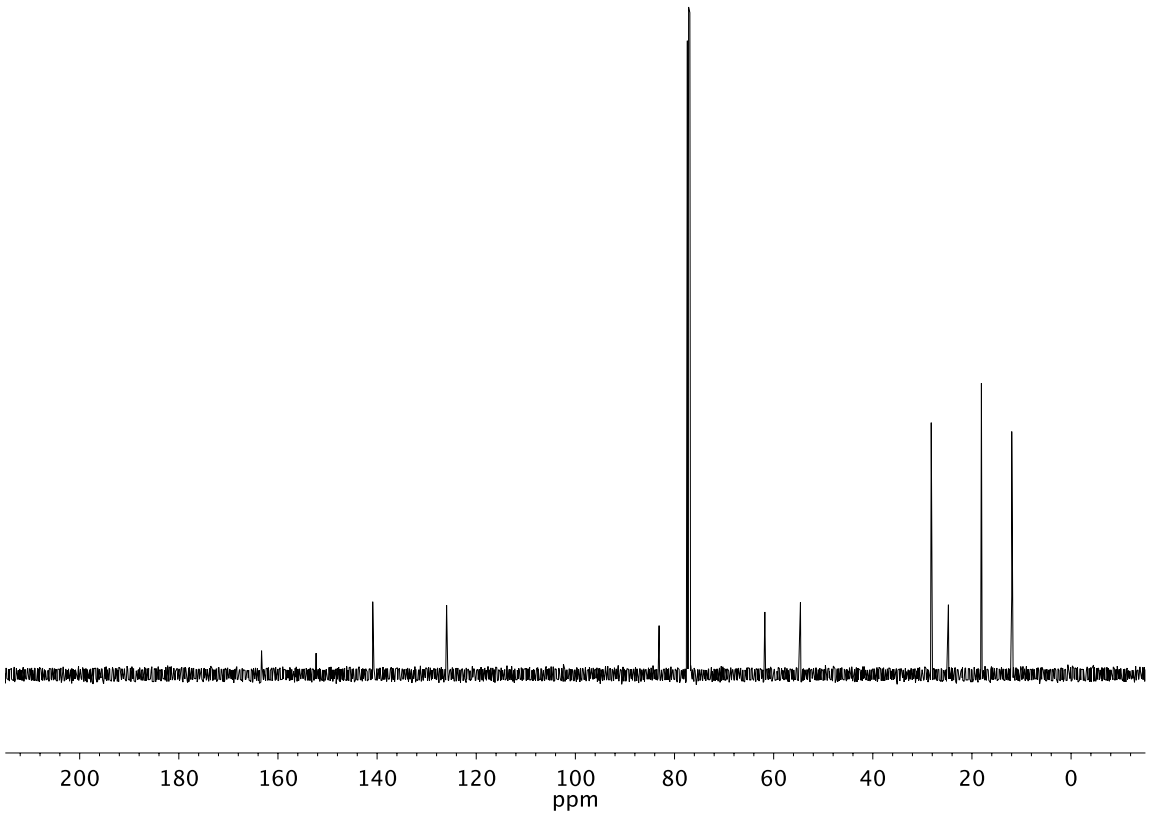

Figure A12.21. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **208b**.

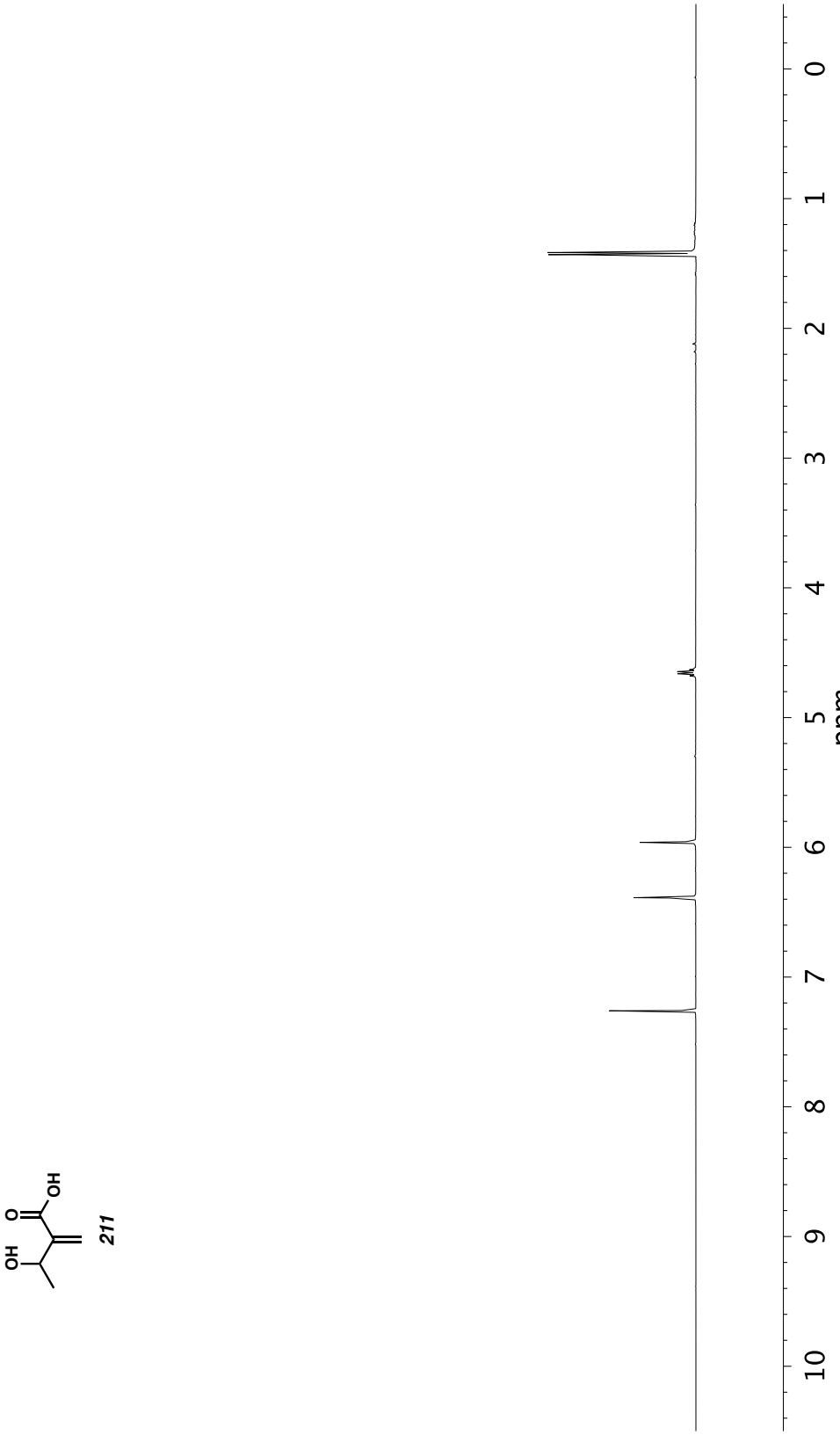

Figure A12.22. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **211**.

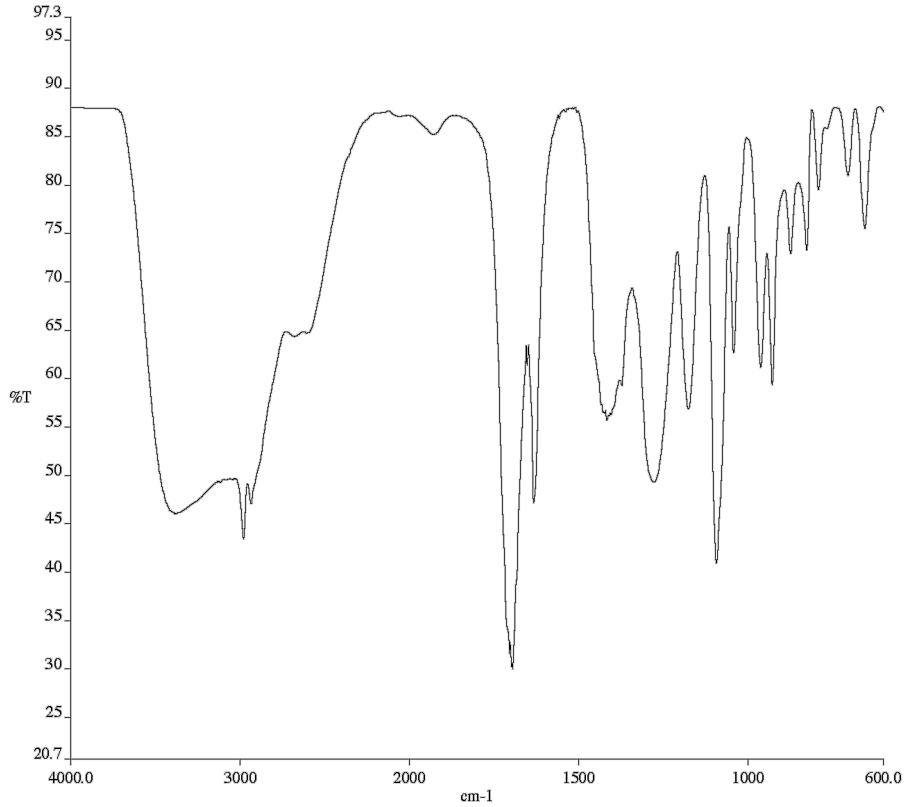

Figure A12.23. Infrared spectrum (Thin Film, NaCl) of compound **211**.

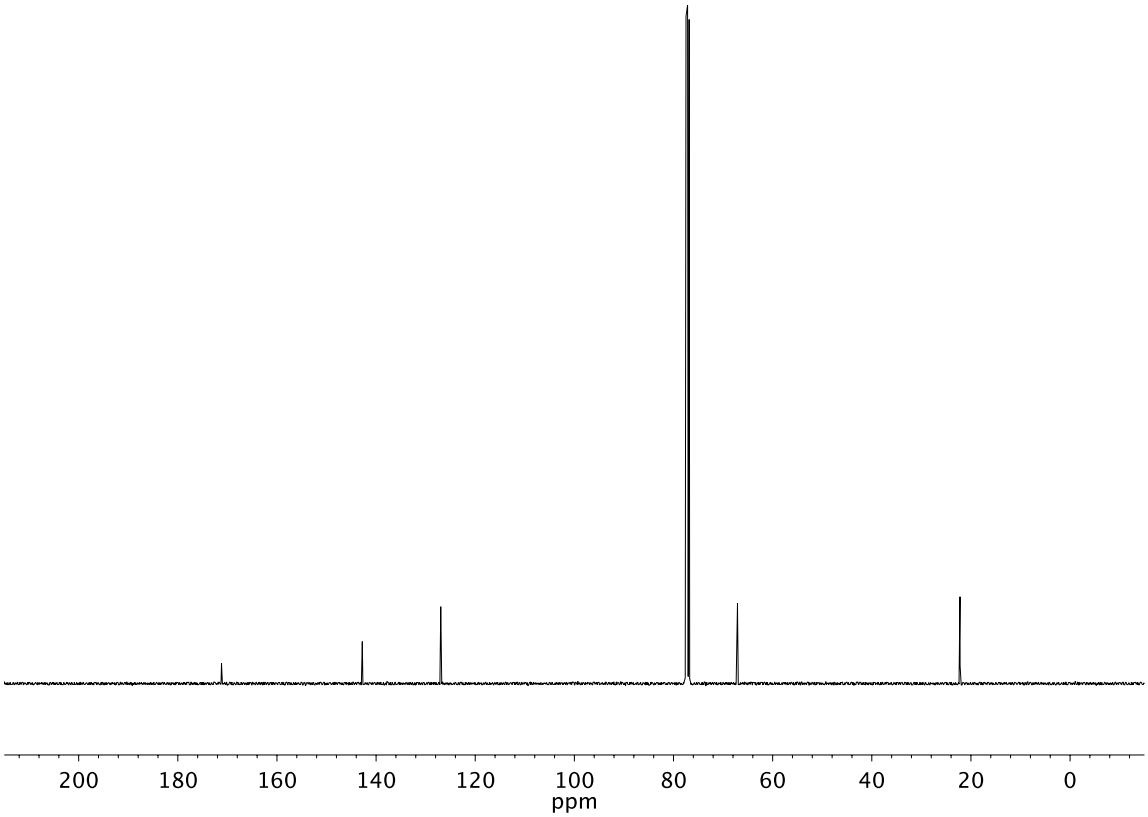

Figure A12.24. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **211**.

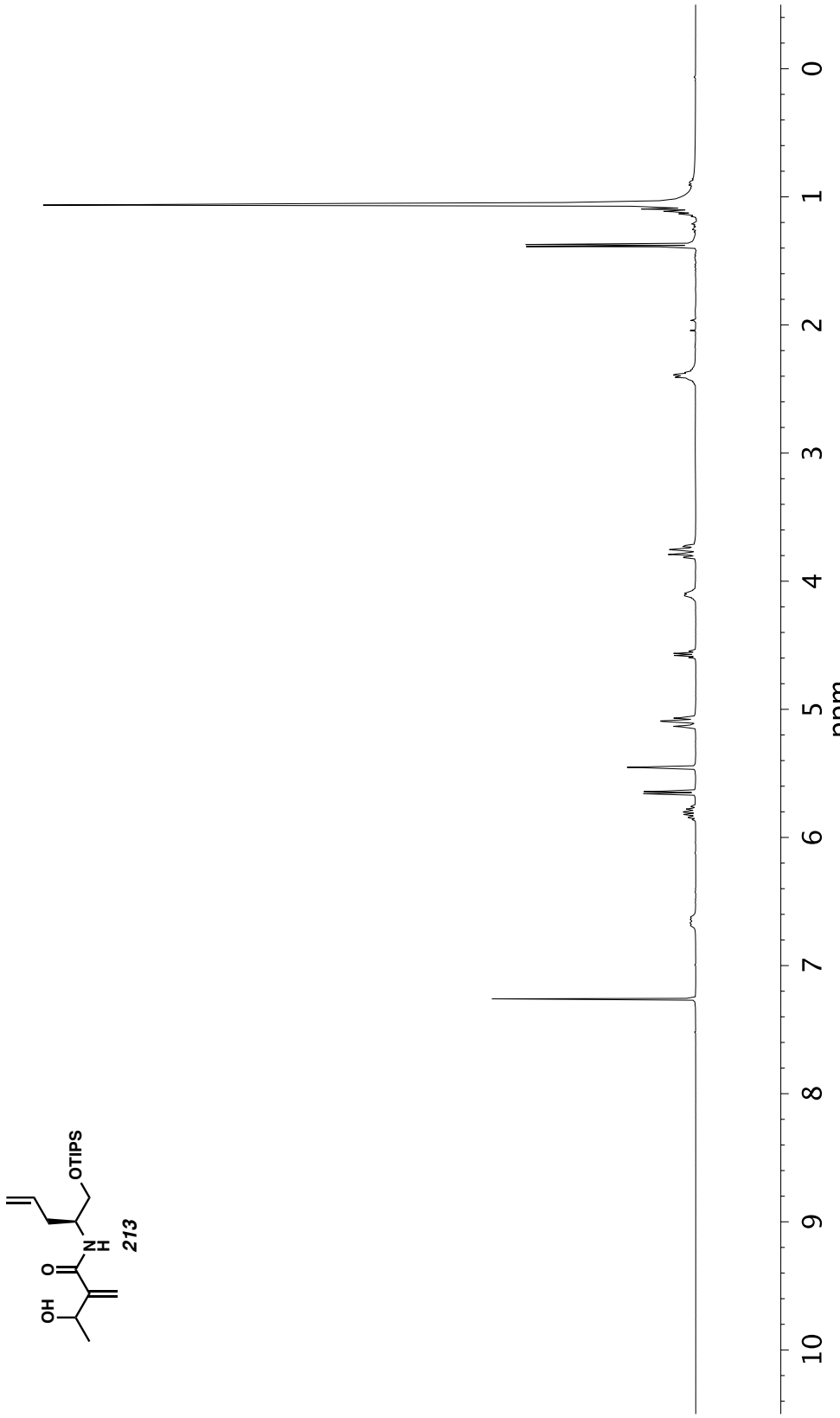

Figure A12.25. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **213**.

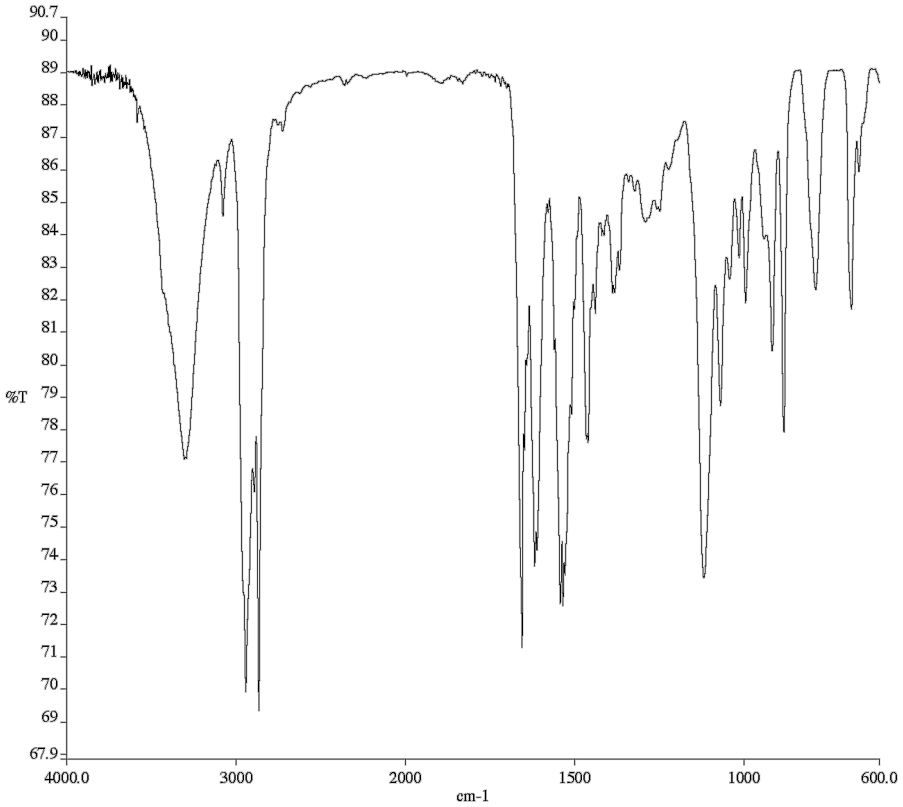

Figure A12.26. Infrared spectrum (Thin Film, NaCl) of compound **213**.

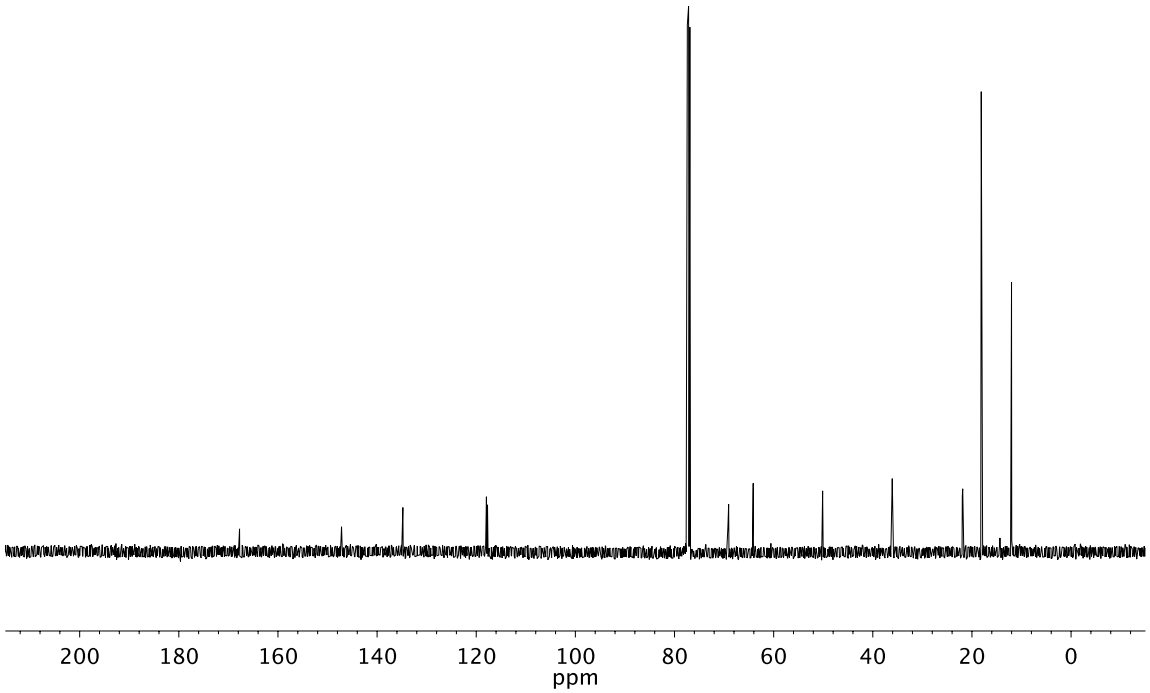

Figure A12.27. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **213**.

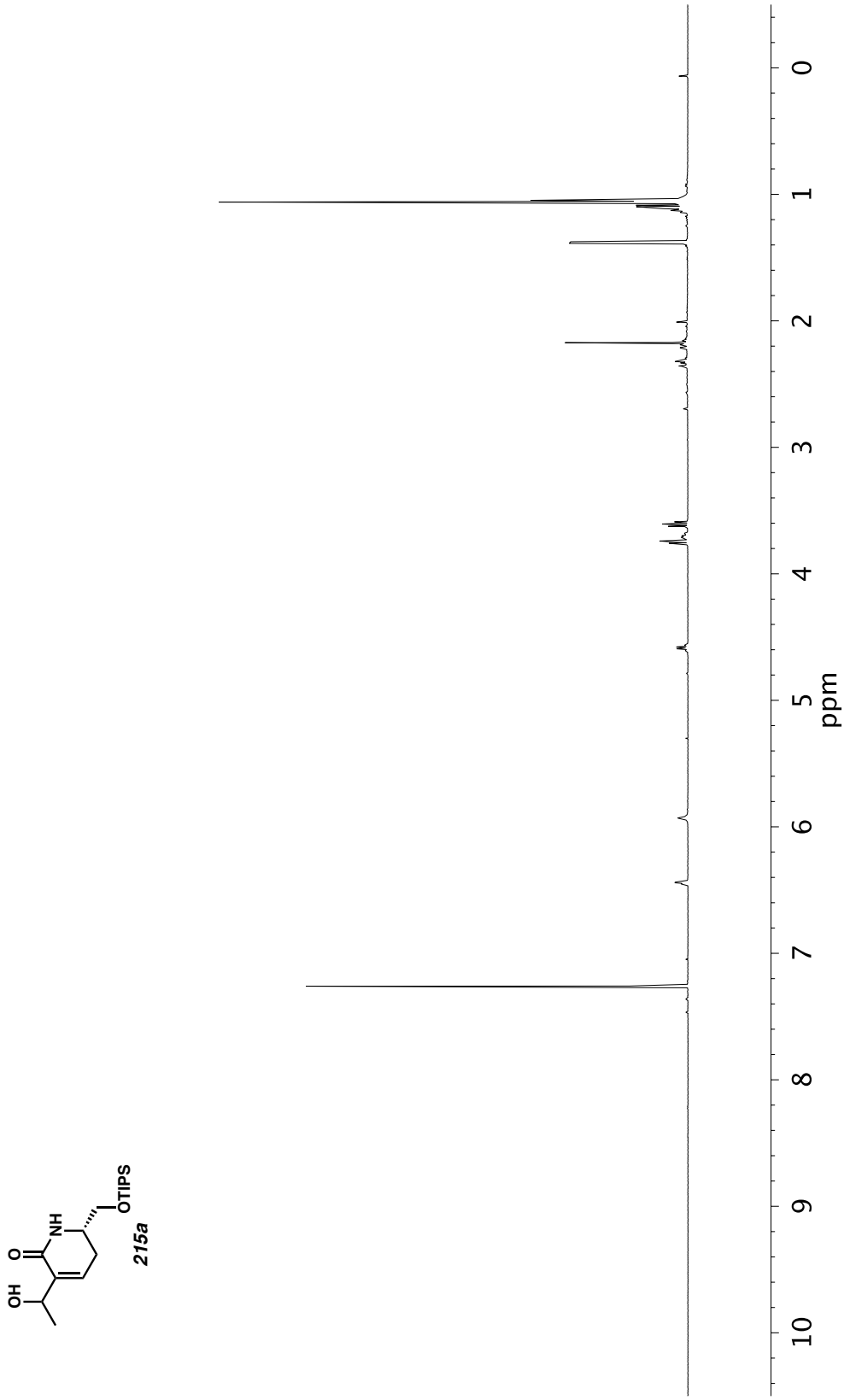

Figure A12.28. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **215a**.

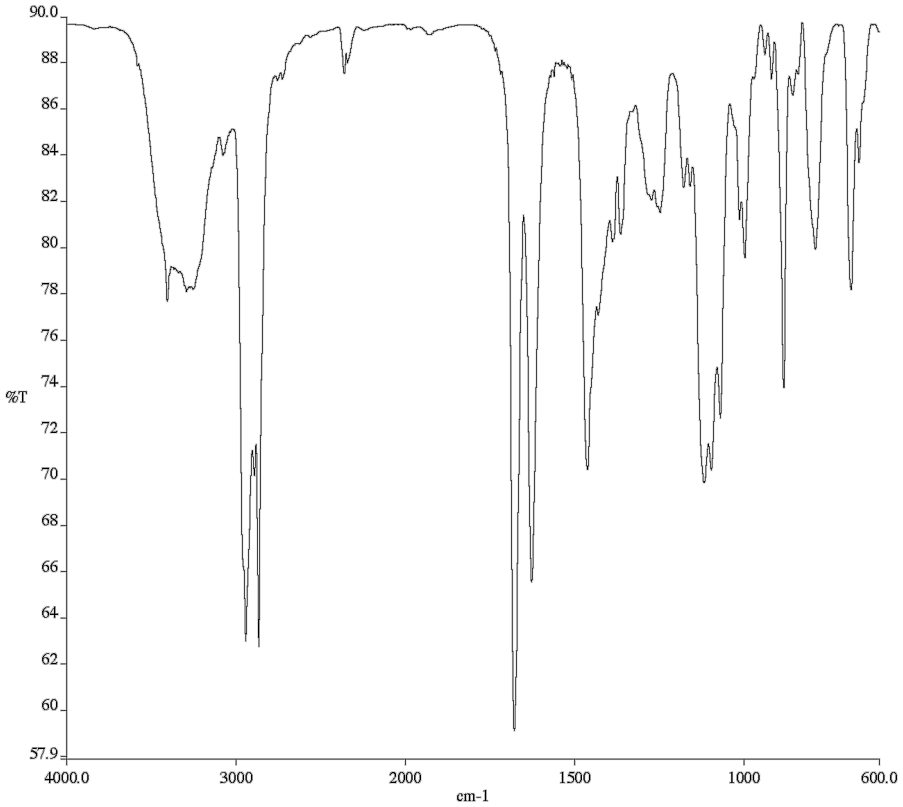

Figure A12.29. Infrared spectrum (Thin Film, NaCl) of compound **215a**.

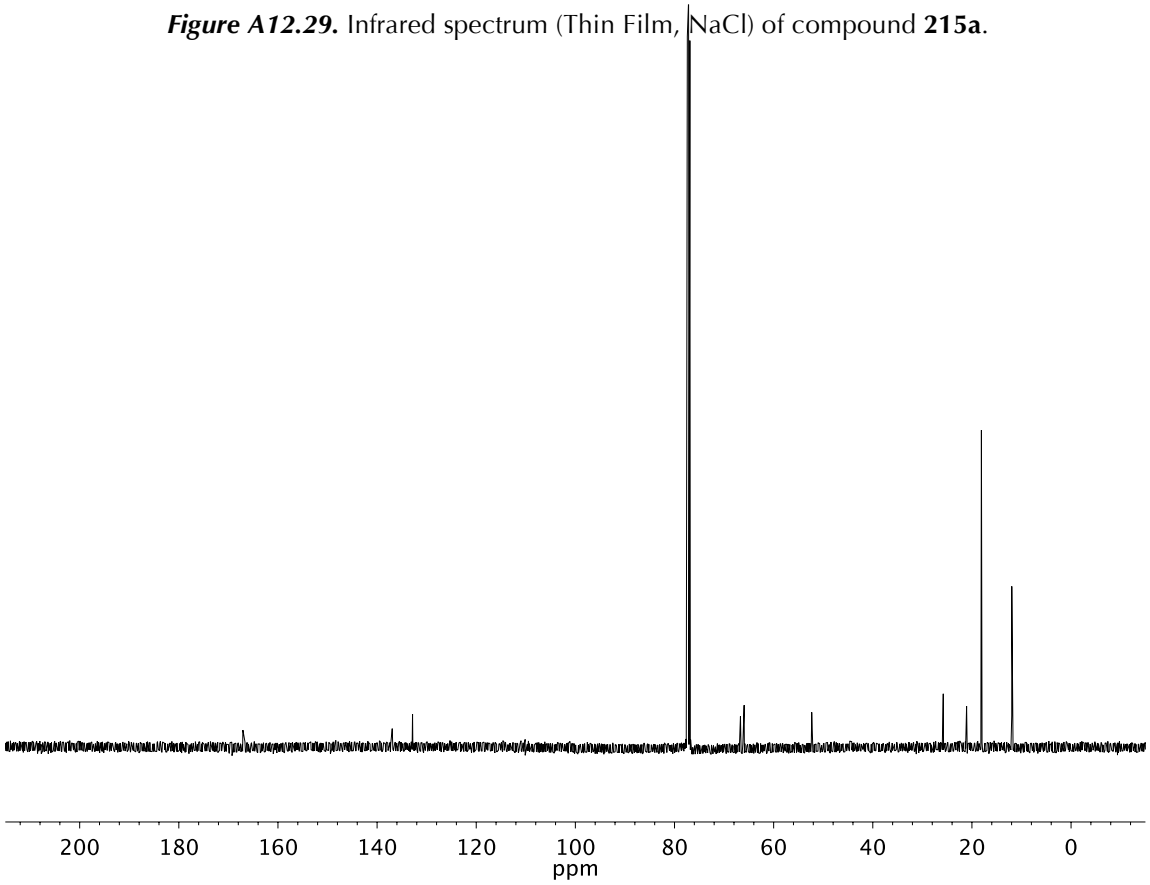

Figure A12.30. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **215a**.

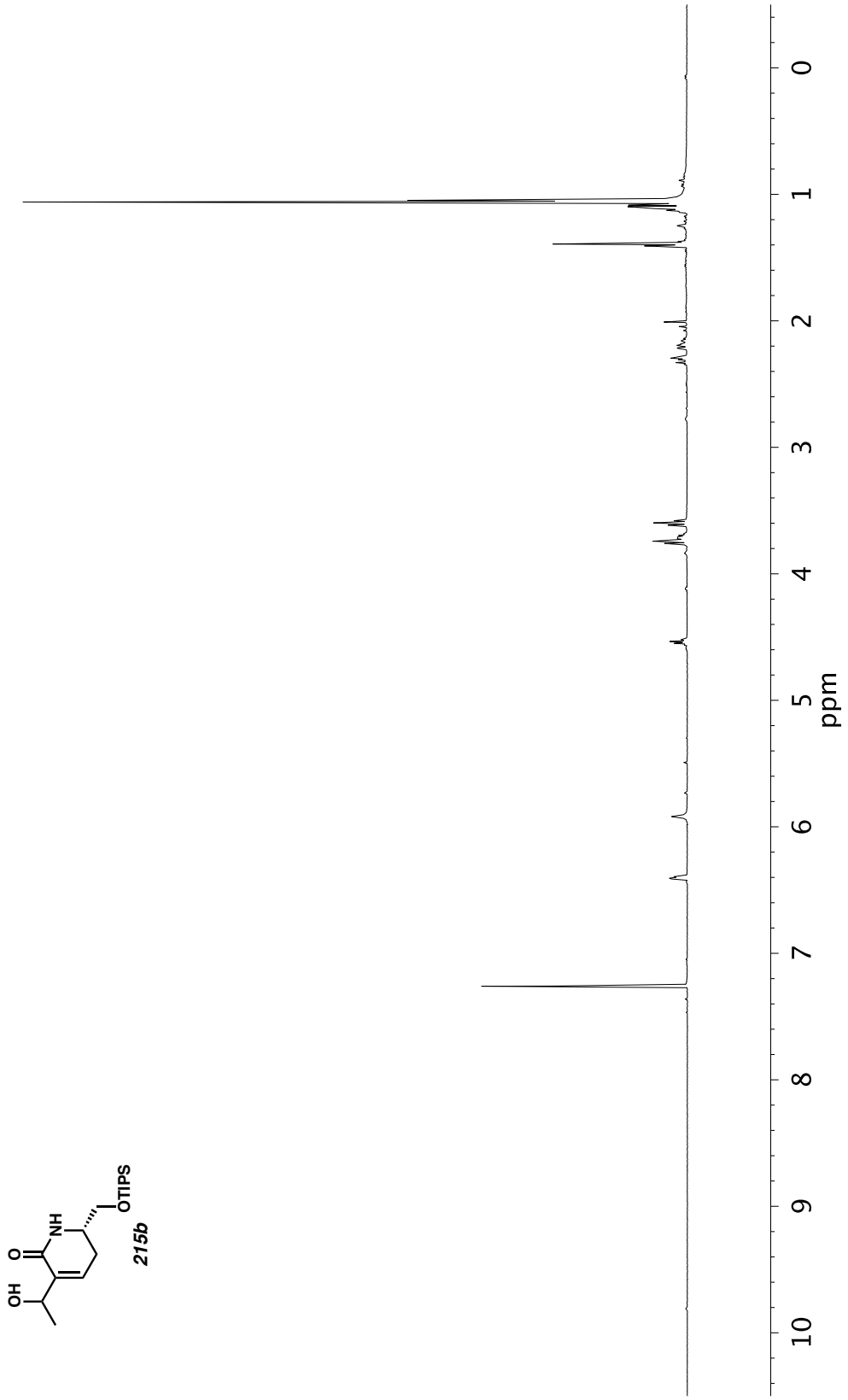

Figure A12.31. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **215b**.

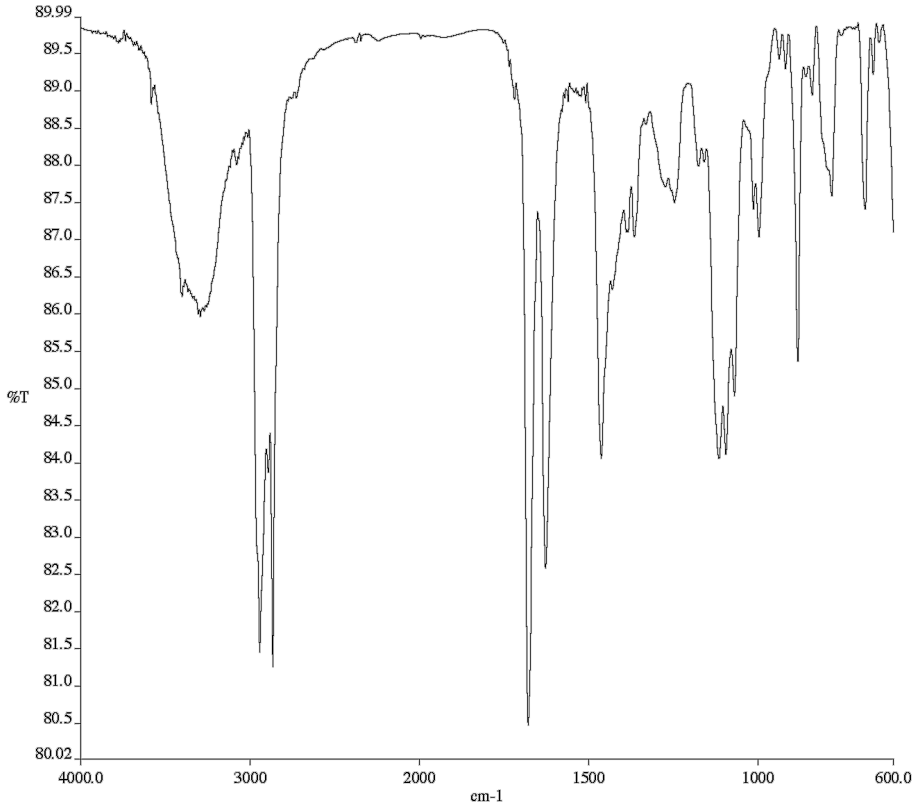

Figure A12.32. Infrared spectrum (Thin Film, NaCl) of compound **215b**.

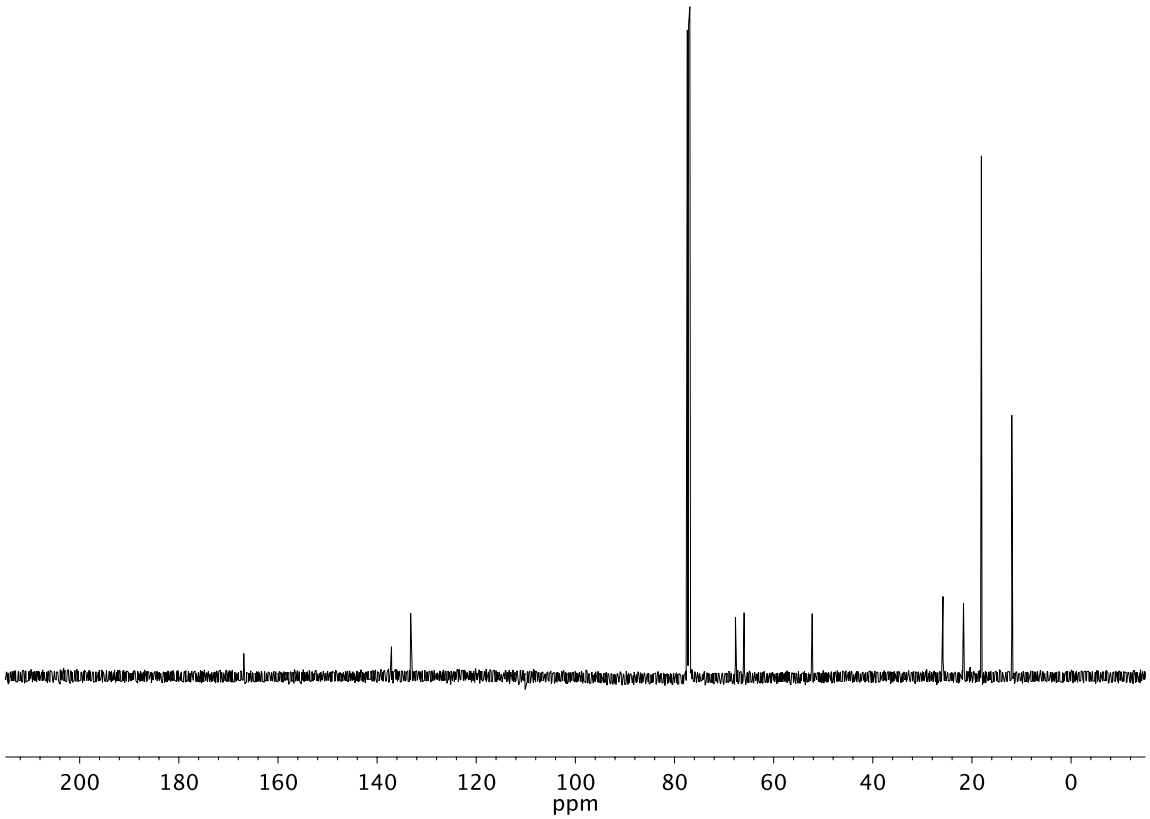

Figure A12.33. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **215b**.